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# CLINICAL MEDICINE



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ANXIETY STATES  
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TOTAL HYSTERECTOMY  
PIROMEN  
SKIN TUMORS  
INTRACTABLE PAIN  
RADIOACTIVE ISOTOPES  
PHENYLBUTAZONE  
FROZEN SECTIONS  
URINARY TRACT INFECTIONS  
ENZYMES  
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1. SIMON, S. W.: ANN. ALLERGY 11: 719, 1952. 2. KESTEN, B. M.: ANN. ALLERGY 8: 408, 1948. 3. LOEW, C. R.: MED. CLIN. N. AM. 34: 351, 1950.

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## Treatment of Anxiety—a Function of the Family Physician

*Therapy is directed along the lines  
of ventilation, reassurance, suggestion,  
reeducation and explanation*

---

JAMES M. NORTINGTON, M.D., *Editor*

It is well known to all thoughtful doctors of large experience that most cases of this psychoneurosis can be well handled by the family physician—if the psychiatrists will only cease and desist from indoctrinating the public with the idea that no doctor other than a psychiatrist can do anything helpful in any case of any vagary of the mind.

A distinguished psychiatrist<sup>1</sup> expresses the same opinion, and, in the good, accurate, understandable language of general medicine, writes an article which forms the basis of this editorial.

What Psychiatrist Luton has said will encourage GP's to keep in their own care most of their patients who become pathologically anxious, and

will, if given proper publicity, make some such patients willing to continue under the care of their own doctor long enough for him to accomplish something—maybe half as long as they would be content to remain under the care of a psychiatrist.

Anxiety in relation to physical disease that brings the patient to the doctor for treatment is normal and protective. Anxiety that leads the patient to go from doctor to doctor, that leads to the discussion of his symptoms with many people, that impels him to read the medical columns in the newspaper as the first topic of the day, that brings him to the physician's office to make frequent minor complaints, that

causes him to be upset by cancer and heart posters, etc.—all these forms of anxiety point to illness in the direction of the “anxiety state.”

Anxiety toward everything is “free floating.” When it is related to some one thing like tuberculosis or cancer, or closed places or high bridges of snakes, it is topical or phobic. When it is overwhelming it becomes panic.

A “basic” anxiety is an underlying emotional reaction to stresses within the individual. Anxiety is differentiated from fear in that the one represents a threat from within that is not clearly discernible, and fear is an emotional reaction to some threat from without that is concrete and observable.

The anxiety state is a definite illness with specific symptoms. It may come on after some catastrophic experience, or follow a long period of stress. It is an extremely frequent pattern of psychoneurosis and there is no physician who does not have several such patients. This is the simplest type of the large group of psychoneuroses. Usually it does not become chronic, being absorbed by, or replaced by, other neurotic symptoms which then place it among the hysterias, phobias, obsessive compulsive, ruminative tension states and the hypochondriases. Any of the chronic organic reactions, such as senile and cerebral arteriosclerotic states and general paresis, may show anxiety-like reactions in their onset and during the course of the psychosis.

The term “anxiety reaction” has recently been adopted to replace the term “anxiety state.” In this condition anxiety is the central symptom which occurs constantly or recurs frequently. It may appear as a general apprehensiveness without any special object or in definite attacks of fear. Such a patient may be

flushed and restless, may perspire freely, pupils may be dilated, hands and body tremulous, breathing shallow, pulse accelerated, tongue and mouth dry, may suffer polyuria or diarrhea, may be nauseated and vomit and may have a total loss of appetite; may show an elevated B.P. increased leucocyte count, raised blood sugar level; sometimes hypoglycemic response, hyperventilation tetany and other metabolic and chemical imbalances.

Rarely does this state remain at the level where the anxiety is “free floating.” The patient may soon develop the fear of dying or of cancer, heart trouble or some other disease, or that he is losing his mind. He has been told that he has no physical disease, so to him it must be his mind. If he is told that he has a mild mental trouble, then the fear becomes: “Will it go into insanity?” He may be unable to go to town or to church or to the movie, or if he goes into any group he must be close to a door. One patient goes walking with her 4-year-old daughter without difficulty; another finds it almost impossible to stay at home unless her husband or mother is there, in spite of the fact that a practical nurse is also with her continuously. This patient has had fear of storms since childhood; her husband built her a concrete storm-cellar which she seeks when a storm is imminent, still in the company of a member of the family. Fears such as of fainting, “going to pieces,” of having people recognize that there is something wrong mentally, fear of going “berserk” and harming someone, are common experiences of the patient who has gone beyond the simple anxiety reaction.

When the personality structure is good, it meets various threats with defenses that are available to all of us. If not so good an anxiety state develops. The behavior soon takes

on the characteristics of another psychoneuroses. If the patient uses the defense of conversion and evasion, his reaction is obsessive-compulsive; e.g., to wash his hands many, many times daily as if to wash away germs or filth or sin. If his defenses are many and of different types he may combine them all in such a reaction as fear of storms or crowds. Other patients find a solution to their problems in symptoms related to the body.

Treatment begins with the first interview. We deal with a person whose very existence is threatened and he needs the security that can be given by his doctor.

Probably it is best for the physician to state at the beginning that he wants to hear all about it. His questions should be simple and designed to stimulate the patient to talk in his own way. Talking it out (ventilation) is of treatment value. If one has only limited time it is well to say so, and to add that it probably will not be possible to get through today. However, it must be made clear that there will be other opportunities for examination and explanation. The patient thus is impressed by an attitude of thoroughness. The first interview should include a careful physical examination with especial attention to any physical responses. As soon as possible all special examinations necessary are to be made.

The physician should control the tone of his voice and his facial expression in order to avoid any suggestion of something ominous. Having the patient wait long to get a report is often agony for him; get examinations done and reported, with reassurance and explanation, as soon as possible.

Is this a purely emotional problem? Could it be the beginning of a

more serious mental illness? What are the precipitating factors? What is in the personality development of the patient that allows him to become sick? A story is obtained from childhood, through school, marriage, business or career, paying attention to any disturbing experiences, explain that the causes of his illness are to be found among the facts of his life adjustment. Interviews may be as short as a half hour and some help may be given if the patient is led into a discussion of his personal life and relationships instead of symptoms since his last visit.

The wife of the patient may show a lack of understanding of his needs or that their interests are divergent. Talks with her are sometimes profitable, again joint discussions frequently lead to better understanding.

Often situations cannot be manipulated to the benefit of the patient, then work toward a better acceptance of the present.

Some medications are useful but should be given with the explanation that they are only given to tide him over the rough periods. Phenobarbital ( $\frac{1}{4}$  gr. t.i.d.) will relieve the tension. Sodium bromide (10 gr. t.i.d.) alternated with something else, also. Tolserol has been found useful to some patients. Prolonged tepid baths may give relaxation, relaxing exercises according to strength and energy, and activities of a recreational nature—sometimes on suggestion from the doctor, in some cases it is better to push him to find activities for himself.

Treatment is directed along lines of ventilation, reassurance, suggestion, re-education and explanation. Physical factors must be considered and treated.

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1. F. H. Luton, *Jour. Tenn. Med. Assn.*, 46:445, 1953.

## SPECIAL ARTICLE

### PRELIMINARY REPORT

# A New Concept in the Treatment of Rheumatic Diseases

*Practical use of enzymes  
in the therapy of arthritis  
and degenerative diseases*

SOLON N. BLACKBERG, M.D., Ph.D., LEILA SAUNDERS  
WALKER, B.S., M.S., Chicago, Illinois

#### INTRODUCTION

Medical science has experienced several ages, each of which in its own way has contributed to the development of new approaches in the treatment of disease. We have experienced the bacteriologic, the vitamin and mineral, the antibiotic, the hormone age; and recently, out of the realization of the importance of enzymes to cell metabolism, has come the enzyme age.

Because of the crippling or fatal effects of certain diseases of unknown etiology, investigators are seeking to discover the secrets of the vital cellular processes. Despite their steadiness in this search for the mechanisms responsible for life

and despite the vast amount of information already contributed, attempts to wholly understand the pathogenesis of disease or to find a lasting form of therapy, in many instances have not been successful. Diabetes, cancer, arteriosclerosis, multiple sclerosis, muscle dystrophy, leukemia and arthritis are only a few of the diseases which are still taking a heavy toll.

In this paper a new concept in the treatment of arthritis is discussed. Until recently, little has been known about the true causes of this group of diseases. The multiplicity of recommended anti-arthritic therapeutic measures is evidence that a cure for arthritis has not yet

been found. Although many agents have been recommended as being remarkably effective in the treatment of arthritis, general clinical use has revealed that in most instances they merely relieve the symptoms and do not usually exert a lasting curative effect. Furthermore, there is a high incidence of toxic effects following the administration of some of these anti-arthritic agents, which include gold, massive doses of vitamin D, cortisone, adrenocorticotrophic hormone, and phenylbutazone. Although, in most instances, the toxic manifestations can be prevented or greatly reduced by proper evaluation of the patients' condition and regulation of the dose in accordance with individual needs, the reported high frequency of these untoward reactions has stimulated rheumatologists to seek therapeutic measures which may be administered safely without interruption during the required course of treatment.

#### AMP IN DEGENERATIVE DISEASES

Recently, a number of papers have reported dramatic results in patients with arthritis and related diseases using adenosine-5-phosphoric acid (a nucleotide present in all cells), which is prepared from muscle. In 1942 Lovgren<sup>1</sup>, in his work with ATP, laid the foundation for the use of the closely related nucleotide, adenosine-5-monophosphate (AMP). Later Rottino<sup>2</sup>, administered AMP in several forms to 60 patients with tendinitis. "Fifty-four of the 60 responded favorably to therapy." "The pattern of response seemed to be relief of pain, return of function, subsidence of swelling, and finally the disappearance of tenderness." The acute cases seemed to be the quickest to respond. It was suggested at this time that AMP

was "possibly curative." Susinno and Verdon<sup>3</sup>, conducted a carefully controlled clinical investigation on the effects of AMP in 36 patients with stubborn chronic tendinitis and bursitis of the shoulder associated with calcium deposits. They administered 20 mg. of AMP intramuscularly daily or every other day. The 36 patients included 15 men and 21 women, with an average age of 49 years. "Thirteen patients with chronic tendinitis were treated as controls, including 3 women and 10 men with an average age of 47.8 years. Eleven of these 13 controls were later treated with AMP and are included in the total of 36 patients treated."

The authors reported that the administration of AMP proved to be easy, safe and was free of side reactions. "Not one severe reaction of any kind was encountered with intramuscular administration of the drug." Therapeutic results were classified on the basis of 1 to 4+. Thirty-one of 36 patients with chronic Tendinitis responded satisfactorily subjectively and objectively (3 to 4+) with an average of 9 injections. Only one of 13 controls responded to placebo injections. "Eleven of these thirteen were later treated with AMP, and 10 obtained good to excellent results (3-4+)."

"The unusually good results in chronic cases of calcified tendinitis for which drastic or prolonged methods of therapy are frequently being resorted to suggest that adenosine-5-monophosphate should be more extensively evaluated as a simple, safe therapeutic modality in calcified tendinitis that is adaptable for routine office use."

Since AMP is known to be essential for all cellular metabolism, it is not surprising that it has distinct

<sup>1</sup> Lovgren, O. *Klin. Wehnschr.* 21:612-613, 1942.  
<sup>2</sup> Rottino, A. *Journal-Lancet.* 71:237-238, 1951.

<sup>3</sup> Susinno, A. M., Verdon, R. E. *J.A.M.A.* 3:239-241, 1954.

therapeutic value in many degenerative diseases other than arthritis. Rottino, Boller and Pratt<sup>4</sup>, found AMP beneficial in the management of patients with thrombophlebitis. A report by Lawrence et al<sup>5</sup>, later verified these results and showed that AMP was effective also in obliterative arteriosclerotic peripheral vascular disease. Miltch et al<sup>6</sup> in a study of atherosclerosis, reported that AMP decreases serum and aortal cholesterol and increases serum phospholipid values in hens where atherosclerosis had developed spontaneously. They showed that AMP markedly reduced the severity of atherosclerosis. Dietrich and Schweigk<sup>7</sup>, administering AMP to patients with severe angina pectoris, reported improvement and stressed the fact that the patients remained symptom-free. Herbrand<sup>8</sup> reported melioration in 35 cases of myocardial insufficiency when AMP was administered.

Shapiro<sup>9</sup> reported improvement in 5 patients out of 10 with multiple sclerosis, treated with AMP and water-soluble vitamins. Improvement occurred in from 3 days to 6 weeks.

In cases of pellagra, Spies et al<sup>10</sup> reported that where nicotinic acid alone is not satisfactory, adenylic acid with nicotinic acid is beneficial. Adenylic acid alone relieved the soreness of the oral mucous membranes associated with pellagra. Bean<sup>11</sup> suggests adenylic acid in the treatment of vitamin deficiencies.

In addition to the therapeutic value of AMP cited above in the treatment of tendinitis, thrombo-

phlebitis, peripheral vascular disease, pruritis and dermatitis, atherosclerosis, angina pectoris, myocardial insufficiency, multiple sclerosis, vitamin deficiencies and arthritis, other benefits of AMP may be derived from its known ability to increase the ATP blood level. Albaum et al<sup>12</sup> showed that the magnitude of ATP level of the blood is increased by the intramuscular injection of muscle AMP and not by yeast adenylic acid. Hawk, Oser and Summerson (1951), too, stress a biological and chemical difference between yeast and muscle AMP. Kornberg<sup>13</sup> in his studies of an enzyme system which contains AMP as a component found that there is a specific requirement for AMP which could not be replaced by yeast adenylic acid.

Since injections of AMP are known to increase the blood level of ATP, directly or indirectly, any beneficial effects of ATP might then be expected from AMP. Both AMP and ATP have been used effectively in polyarthritis, diabetic neuritis and myalgia dorsi<sup>14, 15</sup>. Potter<sup>16, 17</sup> has shown the significance of ATP in cancer. In healthy subjects, growth and glycolysis are interrupted as phosphorylation to ATP is completed. However in cancer, due to enzymic lack, growth and glycolysis continue uninhibited, a condition which gives rise to a continuous growth of the cancer in tissue.

Grenier, Bavay and Lutier<sup>18</sup> studied the efficacy of adenosine triphosphate in chronic progressive arthritis, rheumatic fever, asthma, and gout. They concluded that the results compared favorably with those

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14. Lovgren, O. *Acta. Med. Skand. Suppl.* 165:1945.
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of corticotropin. Furthermore, since ATP increased urinary 17-ketosteroids and decreased the sedimentation rate and eosinophilic count, the authors believed that "adenosine triphosphoric acid may exert a direct effect on the pituitary-adrenal mechanism."

#### METABOLIC ROLE OF AMP

Recent advances made by many investigators including Lipmann, Novelli<sup>19</sup>, Kornberg<sup>13</sup>, and Schlenk<sup>20</sup>, emphasized the metabolic role of animal AMP as a component of certain enzyme prosthetic groups. AMP is known to play an important role in all cellular activities<sup>21</sup> and especially in muscle metabolism. Without it none of the activities of the cell which require energy, such as fat, protein and carbohydrate metabolism, can take place. AMP is directly involved in liberating the energy from cellular foodstuffs by virtue of its incorporation into certain oxidizing enzyme prosthetic groups. It is one of the components of a number of enzymes which are involved in the cellular utilization of carbohydrates and in the oxidation of fats.

For many years it has been generally recognized that "during the early stages of arthritis, deformities result usually from muscle spasm with muscle strain and traumatic joint irritation due to faulty body metabolism." Since the nature of "faulty body metabolism" involved in muscle spasm and atrophy was not known, physical means such as heat, cold, diathermy, underwater therapeutic exercise, massage and drugs such as mephenesin or a combination of physostigmine and atro-

pine were used in therapy. This muscle spasm and other rheumatic symptoms are now thought to be due to an interference with certain enzyme reactions, an assumption which becomes more justifiable with the known importance of AMP as a constituent of certain enzymes directly involved in muscle contraction and relaxation, calcification of bone, and energy liberation for all other cellular activities.

#### CYANOCOBALAMIN

A report by Hallahan showed improvement in 30 of 33 patients with osteoarthritis when treatment with cyanocobalamin<sup>22</sup>. Recently<sup>23</sup>, a number of patients with acute subdeltoid bursitis had been treated with cyanocobalamin. In 5 or 6 weeks most of the patients showed absorption of calcium deposits. The results were considered encouraging and dramatic.

Numerous investigators have reported the effectiveness of cyanocobalamin in a number of systemic disturbances which often accompany chronic arthritis such as anemia, neurologic symptoms, muscle atrophy, loss of weight, and malaise. This vitamin, known as the erythrocyte-maturing factor of the liver<sup>24</sup> has been used effectively in the correction of the relatively resistant form of anemia found in arthritic patients.

Further beneficial effects of cyanocobalamin are shown in various neurologic disorders, such as multiple sclerosis, polyneuritis, and pyramidal tract and spinocerebellar disorders.<sup>25</sup>

Many investigators have reported that cyanocobalamin stimulates growth in children and muscle ef-

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iciency. Ling and Chow<sup>26</sup> recently showed that a major metabolic effect of cyanocobalamin is to maintain the sulfhydryl groups (coenzyme A and glutathione) in reduced form, thereby playing an important role in all stages of growth and development. Corda<sup>27</sup> reports that this vitamin stimulates the production of ATP and increases nucleoprotein formation<sup>28</sup>. Rothman<sup>29</sup> observed a direct correlation between the blood level of adenylyl nucleotide and the erythrocyte count; however, cyanocobalamin effects on erythropoiesis do not parallel the effects of AMP. Sahasrabudhe<sup>30</sup> shows that there is greater regeneration of liver protein in animals receiving cyanocobalamin. This suggests that vitamin B<sub>12</sub> stimulates protein and nucleic acid synthesis. A report by Williams<sup>31</sup> confirms this and shows further that cyanocobalamin affects protein metabolism through its ability to activate transmethylation by the enzyme transmethylase. It is thought that this enzyme may use vitamin B<sub>12</sub> as a "co-factor." Cyanocobalamin is also utilized by bone marrow cells. It corrects an abnormality in cell nucleic acids in persons with pernicious anemia in relapse.<sup>32</sup> These investigations suggested a possible functional interrelationship between cyanocobalamin and AMP.

#### CLINICAL EVALUATION

Because the action of one constituent apparently supplements or enhances the action of the other, it has seemed advisable to combine cyanocobalamin with muscle AMP in

the treatment of patients with arthritis and related diseases.

A panel of six well qualified clinicians was chosen in an attempt to evaluate the ability of AMP and cyanocobalamin (Cobaden\*) to arrest and correct the rheumatic process.† In order to minimize misinterpretations of the results due to spontaneous alterations in the course of the disease and to eliminate as far as possible individual variations in evaluating the therapeutic response, each clinician worked independently, but at intervals was given an opportunity to see and discuss the results obtained by the other members of the panel. A preliminary report of the clinical findings in the first 70 patients has been published by DeLucia *et al*.<sup>33</sup> These patients with osteoarthritis, polyarthralgic pain, polyarthritis, tendinitis (bursitis), musculofasciitis, tenosynovitis, peripheral neuritis (sciatica), and diabetic neuropathy had failed to respond to prior treatment with analgesics, hormones, or physical methods. "Treatment was successful in terms of pain-relief, restored mobility, and diminished swelling and tenderness in 66 of the 70 patients." In this preliminary report no attempt was made to explain the chemical changes or physiologic alterations effected by the therapeutic agent. Clinical and laboratory studies are being continued on a larger group of patients in an attempt to gain a better understanding of how these agents affect the rheumatic process.

The purpose of the present report is to summarize some of the important advances made by previous investigators together with the data

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27. Corda, G. *Bull. Soc. ital. biol. sper.* 28:1935-7, 1952.

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30. Sahasrabudhe, M. R., Rao, M. V. *Nature.* 168: 605, 1951.

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32. Horrigan, Jarrold, Vilter. *J. Clin. Invest.* 30:31, 1951.

33. DeLucia, F. A., Strosberg, I. *Med. Times.* 82:1, 1954.

\* This combination of AMP and cyanocobalamin, under the trade name Cobaden, was furnished by The Rand Pharmaceutical Co. Inc., of Rensselaer, New York.

† Blackberg, S. N., DeLucia, F. A., Strosberg, I., Engel, J., Meckler, A. A., and Markowitz, B. F.



obtained from our own studies, and to set forth the biochemical role of cyanocobalamin and adenosine-5-monophosphate in rheumatic disease therapy. A search of the recent literature has brought to light the importance of enzymes, not only in normal cellular activity, but as a new effective weapon for combatting a wide variety of diseases. The pendulum seems to be swinging through the entire gamut of known exogenous anti-arthritis agents, and is coming to rest in a new concept of anti-rheumatic therapy based on the advances of cytochemistry.

Along with the increasing importance of enzyme components in the treatment of disease have come recent advances in enzymology which have helped us to understand the *in situ* action of the vitamins, minerals, amino acids and hormones and their relationship to enzyme activity. We have known that each one is important in metabolic activities; but the fact that all of these components and perhaps more, actually become part of one system functioning to do a specific cell job, is an interesting and meaningful conclusion. We find that the amino acids actually make up the enzymes of the cell, that vitamins become a necessary part of certain enzymes, that certain minerals activate enzymes; and now it is easy enough to conceive a model of an enzyme with a steroid as a prosthetic group<sup>34</sup>.

Life and disease are taking on new meaning. Life on one hand is now defined as an orderly functioning of enzymes, while disease on the other hand is thought to be the result of a disorder of enzyme function<sup>35</sup>. With this approach, complete enzyme studies of normal and diseased cells have begun. It is neces-

sary to know all the enzymes involved in life, what they do, what forms them, what makes them work, what defective enzyme reactions are responsible for disease, and why the reactions are defective. This is the basic work of this enzyme age.

#### THE ROLE OF ENZYMES

It is reported that "the basic operations of life are built around the necessity of getting a variety of chemical compounds such as simple sugars, amino acids, vitamins, and minerals into all cells of the body. This involves the breaking down of the ingested foodstuffs into small enough particles (molecules) and the delivery of these molecules to the cells."<sup>36</sup> Although enzymes are necessary in digestion, their role in cell metabolism is just as important. All chemical reactions which take place in the cell require these catalysts. Enzymes are therefore considered to be the fundamental units of life<sup>37</sup>. They are catalysts of high molecular weight, protein in nature and are found in organized portions of the cell such as microsomes and mitochondria. They are found in all cells, and in fluids such as plant sap, blood plasma, saliva, gastric juices, urine and milk.

The substances on which enzymes act are substrates. Some enzymes act without added groups; others need a prosthetic or conjugated group which is necessary for their activity. Enzymes participate in reactions but they reappear in their original form. In this way a small amount of enzyme or catalyst can perform an extraordinary amount of chemical conversions. Enzyme action is very specific since it is not only limited to one type of reaction, such as the hydrolysis of a certain linkage, but to only a few individual substrates, and in some cases to

34. Dorfman, R. J. *Vitamins and Hormones*, Vol. X, p. 366. Ed. R. Harris, Academic Press, 1952.

35. Potter, Van R. *Enzymes, Growth and Cancer*. P. 6, Charles C. Thomas Publisher, 1950.

36. Potter, Van R. *Ibid.* P. 11.

37. Sumner, J., Myrbach, K. *The Enzymes*. Vol. I, Pt. 1, p. 1. Academic Press, 1950.

one substrate. The fate of a given compound delivered to a cell is not determined solely by the nature of the compound. Any given compound can participate in a variety of chemical transformations; hence, every compound taken into a cell is confronted with a number of alternatives depending on the needs of the cell, or better, on the active enzymes present. For example, pyruvate, formed during carbohydrate decomposition may undergo many stages of transition; it may form lactic acid if given 2H groups, with a phosphate group, it can form phosphopyruvic acid, an added amino group will produce alanine, a  $\text{CO}_2$  group will form oxaloacetic acid, subtracting a  $\text{CO}_2$  group leaves acetaldehyde or taking away 2H forms  $\text{CO}_2$  and acetic acid. Amino acids also have alternate pathways. They may combine with other amino acids to form protein or may be deaminated to form  $\text{NH}_3$  and a keto acid. This shows that the fate of compounds entering the cell "is not predestined to be used in a particular way"...

"Any given compound entering the cell may not have all the alternatives open to it...a molecule entering a cell may be burned as fuel, used for growth or maintenance, or used as a building block for the synthesis of a special chemical product. Any individual molecule may pursue one alternative or the other, but some of the molecules of a given compound may take one alternative while other molecules follow another pathway," depending on the active enzymes present. It is easy to visualize the living cell as a "purposeful, self-maintaining, self-perpetuating association of enzymes that directs chemical processes along specific lines according to the needs of the organism."<sup>38</sup>

38. Potter, Van R. *Enzymes, Growth and Cancer*. P. 14, Charles C. Thomas Publisher, 1950.

Enzymes are classified on the basis of their substrate specificities. For example, dehydrases are those enzymes which remove water, desulfurases remove hydrogen sulfide, hydrolases are hydrolyzing enzymes and dehydrogenases remove hydrogen. To the dehydrogenases belong prosthetic groups which contain AMP. The action of certain enzymes may be described as a transfer of a radical or group from one substance, the donor, to another substance, the acceptor. Some enzymes are classified according to their prosthetic group, as the flavin enzymes which contain riboflavin, the copper enzymes which contain copper, etc.

Enzymes in the living organism should be thought of as a group, working together as a system. In the G.I. tract, first one enzyme then another hydrolyzes proteins to peptides; then others continue the process down to the amino acids. The reaction products of one compound become substrates ready for the action of other enzymes. The same enzyme teamwork exists in the metabolism of other foodstuffs. In the cell glycogen is broken down to  $\text{CO}_2$  and water by a large group of enzymes. To form water, hydrogen is removed by a certain group (dehydrogenases), and then is transferred to oxygen by way of other groups (coenzymes I and II, the flavin enzymes and the cytochromes). It may be understood then that if a group of enzymes is nonfunctioning, intermediate products can accumulate which in time may be directly or indirectly deleterious to the cell, to the organ and its function. If this condition is not corrected, disease results. Medical science has assigned specific names to metabolic disturbances in different tissues, although the general etiologic processes may be similar.

## NATURE OF ENZYMES

Enzyme activities depend on the hydrogen ion concentration of the medium in the cell. Maximum activity occurs at a rather narrow pH range. As a result, experimental work with isolated enzymes often requires the use of buffer solutions. Since enzymes are proteins, and are therefore ampholytes which change their state of electrical charge in the various pH regions, it becomes obvious that their activities are greatly influenced by pH. Enzyme activity responds also to changes in temperature. Each enzyme has its own temperature optimum as well as its own temperature of inactivation. Most of them are inactivated at the same temperature which denatures protein, 60°C.

In each case every pure enzyme isolated was found to be a simple or conjugated protein. Because little is known about protein structure, not much light can be thrown on the chemical nature of enzymes. Where no prosthetic group, no metal or light absorbing group had been found, these enzymes were called simple proteins. It is thought that certain groups in the amino acid molecule of the enzyme proper combine with the substrate and therefore are responsible for its specificity.

## COENZYMES, ENZYMES AND ACTIVATORS

Coenzymes are dialyzable substances required by certain enzymes for their specific activity. Upon dialysis such an enzyme system breaks down into its two component parts (enzyme and coenzyme), which are inactive when separated, but upon combination become active again. The non-dialyzable protein component is the enzyme proper. The dialyzable relatively heat-stable, non-protein part is the coenzyme or prosthetic group, which dissociates easily. We build our own enzyme sys-

tems and can make some of the constituents but not all. For example, we must be provided with certain amino acids which we cannot synthesize—the so-called essential amino acids. On the other hand, we can form some amino acids. For the building of the prosthetic groups, specific essential compounds must be available. The best known of these essential components of co-enzymes are vitamins, minerals, trace elements, and nucleotides such as AMP, ADP, and ATP. It appears now that lecithin is also an integral part of certain enzymes.<sup>39</sup> These essential components are necessary for the action of the enzymes to which they are attached. In many cases, a vitamin or vitamin derivative attached to the nucleotide of which AMP is a component, acts as a coenzyme. It is suggested that the probable role of all vitamins is that of a component of certain enzyme prosthetic groups.

Some enzymes occur in nature in an inactive state but are activated by a change in pH, by the action of other enzymes upon them, or by the presence of divalent metallic ions such as Mn, Co, or Mg. These enzymes are thought to combine with their substrates through these metallic ions. Other enzymes may be activated by anions.

It is easy to see then, that enzymes do not act alone. Vitamins, specific ions and nucleotides are known to be necessary.

## ENZYME INHIBITORS

Some enzymes are inhibited by the presence of certain ions or chemical agents. This is important in the processing of AMP. Attention was called to the fact that many "chemically pure" commercial preparations

<sup>39</sup> Kieley, Meyeroth. *J. Biol. Chem.* 183:391-401, 1950.

of AMP and ATP contain contaminants or inhibitors which are not detected by methods used to determine its chemical purity. These preparations, when tested in a biologic system have very little if any activity. It is necessary then to use a preparation that is biologically active as well as chemically pure.

It should be noted that only AMP which has been proven biologically active and free of inhibitors can be expected to give the desired therapeutic effects<sup>39a</sup>. The AMP in Cobaden is tested both chemically and biologically and is certified to be free of inhibitors.

#### SUMMARY

Thus far a number of reports were discussed on the use of AMP and other components of certain enzyme prosthetic groups in the treatment of a wide variety of conditions. Its effectiveness in these diversified disturbances suggests that AMP plays an important role in over-all body metabolism. Its role in the metabolism of fats, carbohydrates and proteins is vital since it is here that energy is produced for all bodily functions. That energy is needed for all cellular activity has long been known, but the concept that AMP, as a coenzyme constituent, is an essential link in the chain of normal cell processes is new. It helps us to understand how any disturbance resulting in a lack of AMP or other enzyme constituents may have a casual relationship with the many rheumatic disorders and directly or indirectly with other degenerative disease processes.

We have shown that enzyme systems are dependent not only on the enzyme proper but may need other constituents such as nucleotides (AMP), vitamins, amino acids,

minerals, lecithin and probably hormones. The therapeutic value of these constituents has been established for many years, but their specific roles or modes of action have not been understood until the recent discovery of their relationship to enzyme systems.

Authoritative information has been presented to show the therapeutic parallelism between cyanocobalamin and AMP. It is now thought by some investigators that cyanocobalamin (vitamin B12) may be a component of an enzyme also.<sup>40</sup> Adenylic acid, now definitely established as a prosthetic group component, was once classified as vitamin B<sub>5</sub>.

Cyanocobalamin is effective in a wide variety of conditions such as pernicious anemia, peripheral neuritis, diabetic neuritis, sprue, alcoholic diabetes, nutritional neuropathies, multiple sclerosis, polyneuritis, pyramidal tract and spinocerebellar disorders, and osteoarthritis. It is known also to promote growth in children.

This therapeutic parallelism which exists between AMP and cyanocobalamin is the basis for the use of this combination (Cobaden) in the treatment of arthritis and related diseases. It proved effective in 94% of the 70 patients with arthritis, bursitis and other rheumatic disorders.

With each advance in the knowledge of cell chemistry and the structure and function of enzyme systems, we come closer to a definition of life and to a better understanding of the etiology, pathogenesis and treatment of disease. Replenishing the cells with the molecular components necessary for normal cellular activities is therefore the basis of this new approach to disease therapy and with it, the birth of a new age in medical science.

39a. LePage, G. A., Potter, Van R. J. *Biol. Chem.* 179:1229, 1949.

40. *Ann. Intern. Med.* 35:521, 1951; *Physiol. Rev.* 32:85, 1952; *Nut. Rev.* 7:165, 1949.

## ORIGINAL ARTICLES

### Total Hysterectomy

*Removal of the uterus together  
with its cervix has many advantages  
over subtotal hysterectomy*

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One of the notable advances in gynecologic surgery that has been made in the past few years is the general acceptance of the concept that when hysterectomy is indicated it should be total hysterectomy, whether abdominal or vaginal. Until recently the greater number of hysterectomies performed were subtotal. Gradually, as technical proficiency and experience were acquired, more and more gynecologists have come to believe that in almost all cases it is preferable to remove the uterus together with its cervix. Such an operation has many advantages over subtotal hysterectomy.

#### ADVANTAGES OF TOTAL HYSTERECTOMY

In the first place, it eliminates

the possibility of the development of cervical or endocervical neoplasms. This is an important consideration today, when the indications for hysterectomy have been extended and the operation is being performed on younger women, because it means that these women have a longer time to live with their cervix and therefore there is more chance of the retained cervix undergoing malignant changes, too often long after the patient has forgotten about it being present. The incidence of carcinoma in the retained cervical stump has been estimated to be as high as 3 per cent.

Another advantage of total hysterectomy is that it eliminates the possibility of the development of in-

tractable discharges and vaginal bleeding usually from endocervical polyps. Such symptoms are a constant annoyance to the patient, who may even become extremely apprehensive about them.

Finally, total hysterectomy assures the patient that pelvic pain from infection in the retained cervical stump will not develop. In the performance of subtotal hysterectomy there is interference with the blood supply of the cervix and frequently the chronic cervicitis already present becomes more widespread and produces discharge, pelvic pain, backache and dyspareunia. Cauterization or conization too often produces a stricture of the external os with resulting pyocervix.

If the cervix is not removed when the uterus is excised, it is important to warn the patient of the possibility of the development of malignant changes in the cervical stump, manifested by discharge or pain. Moreover, she should be urged to return for periodic examinations and if symptoms are progressive or pathologic changes are taking place in the cervix, she should be urged to have the cervical stump removed. The only treatment of the diseased cervical stump is vaginal surgical excision. Cauterization, conization or amputation of the retained cervical stump cannot be considered adequate treatment, and indeed, as mentioned earlier, may cause stricture of the external os.

By total hysterectomy we mean excision of the uterus including its cervix, but not removal of the adnexa. Total hysterectomy has become a popular term which to many of the laity means removal of all pelvic organs. Then, too, I have seen women who could not understand why they were having symptoms when they believed they had had a total hysterectomy, only to find on

examination a lacerated or hypertrophied and infected cervical stump.

Removal of the adnexa in a woman with normal ovaries who has not yet undergone the menopause, under the guise of the possibility of the development of future malignancy, is to be condemned. The undesirable and too often severe and abrupt artificial menopausal symptoms plus the psychic problems that develop make it mandatory that they be left intact.

#### INDICATIONS

The indications for hysterectomy have been extended and in many instances excision of the uterus has replaced other forms of therapy for pathologic changes and symptoms in the female pelvic organs. Fibroids continue to be the most common indication for hysterectomy and this is to be expected because of the frequency with which these benign tumors develop in the uterus. It is my belief, that when treatment for fibroids is indicated and because of symptoms, age, childbearing or size myomectomy seems unwise, then hysterectomy and not roentgen-ray or radium therapy is indicated. When these tumors are causing symptoms the intelligent modern woman wishes not only relief from symptoms but also reassurance that in the future symptoms will not recur and that a malignant lesion is not going to develop—not from the fibroid but from a uterus that contains fibroid tumors. Small asymptomatic fibroids do not require treatment in a woman of any age. This is especially true in young women. However, if such tumors show rapid growth, produce menstrual disturbances, or after careful investigation are considered to be a barrier to conception or the cause of repeated abortions, then myomectomy is indicated.



*Pelvic endometriosis* is too often used as an excuse for hysterectomy along with ablation of normal ovaries. However, if extensive pathologic changes from this condition produce symptoms that warrant radical surgical treatment and future pregnancies are not possible, then the uterus should be removed at the same time that other necessary pelvic procedures are carried out.

In this day of the wonder drugs *pelvic infections* are so well controlled that they rarely require surgical treatment. In the occasional case, however, it becomes necessary to remove the adnexa because of abscess formation and in such cases hysterectomy should be mandatory.

The largest group of cases for which hysterectomy has become so popular is composed of women whose families are complete or who have undergone the menopause and present *extensive cervical injuries, infection and menstrual disturbances*. In such cases total hysterectomy is the treatment of choice. I am opposed to such formerly popular "conservative" measures as conization, amputation of the cervix, defundectomy or application of radium. Such measures might relieve their symptoms, but they will not prevent recurrence of symptoms or development of a new set of symptoms referable to pathologic changes that could terminate in malignant changes.

There is another group of patients in whom hysterectomy would seem advisable. This is the group of women in whom sterilization by tubal ligation is indicated because of *repeated cesarean sections*. If they have a history of menstrual disturbances, previous toxemias of pregnancy, evidence of hypertension or renal changes, or pathologic changes in the uterus such as fibroids, it would certainly seem prudent to re-

move the uterus at the time of cesarean section rather than ligate the tubes. This would eliminate the possibility of future pelvic surgery being required.

#### VAGINAL OR ABDOMINAL APPROACH?

Although total hysterectomy is almost universally accepted today as the ideal method when excision of the uterus is indicated, there still remains some question as to the preferable surgical approach to the uterus. This confusion is unwarranted since the indications for each approach are entirely different. The correct decision may be reached after a thorough history has been taken and a complete physical examination has been made. Selection of the approach should be based on the pathologic alterations found, whether or not previous pelvic operations have been performed and the presence or absence of obesity. Too often, the surgeon's decision is influenced by his technical proficiency or his personal preference for one or the other approach. Obviously, such practice is to be deplored. For this reason, the surgeon should be equally adept in the performance of hysterectomy by either route so that his decision is not influenced by this factor.

The *vaginal* approach is indicated in women with uterine prolapse, especially those of extreme degree, and in obese women with a freely movable uterus and some degree of prolapse. It is my belief that the vaginal approach is contraindicated in women with fixed pelvic structures or in those whose cervix cannot be drawn down to the vaginal outlet.

There have been some who have objected to the vaginal approach because they say that it results in shortening of the vagina or prolapse of the anterior vaginal wall. However, these conditions were not found

at postoperative examination of 430 women in whom vaginal hysterectomy was performed by me. The only complications which sometimes occur are those referable to the urinary tract. The end results of the vaginal approach are excellent and the incidences of postoperative shock and distention are less than following the abdominal operation.

The *abdominal* route should be employed in the majority of women requiring hysterectomy. Indications for abdominal hysterectomy include malignant lesions of the pelvic organs, large uterine fibroids, a history of previous laparotomies, endometriosis and previous pelvic infection. The abdominal approach has a number of advantages over the vaginal route. For example, in women with extensive adhesions, hysterectomy is easier to perform by the abdominal route. Also, by this route injuries to the bladder and ureters are less likely to result. Finally, if a diseased appendix is found, it can be removed at the same time so that a second operation is obviated. Complications are probably more numerous after the abdominal than after the vaginal route, but it is also true that the diseases for which the abdominal approach is required are more serious than those for the vaginal route.

#### MEANING OF HYSTERECTOMY

It is always wise to explain not only to the patient but also to her spouse exactly what hysterectomy entails. Both should be told that

hysterectomy with preservation of the adnexa does not precipitate the menopause, that annoying symptoms will not develop after hysterectomy and there will be no need for becoming addicted to hormones. Patients want to be reassured that their sexual life will not be disturbed following excision of the uterus. Finally, they should be told that obesity need not develop following hysterectomy.

#### A GYNECOLOGIC PHILOSOPHY

As experience accumulates in the teaching and practice of clinical gynecology it is natural for a gynecologic philosophy to evolve. In conclusion, it would seem appropriate to summarize briefly my own philosophy. A properly performed total hysterectomy is the treatment of choice for the woman in good physical condition past the child-bearing age with extensive obstetrical injuries, a damaged and diseased cervix, and menstrual disturbances. Repeated unnecessary operations are being carried out today on a large part of our female patients under the guise of conservatism. Menstruation is not necessary for life and health. Moreover, such inadequate pelvic surgery leaves the patient unable to conceive, but liable not only to the development of new but also the recurrence of previous symptoms, such as pelvic pain, hypermenorrhea and polymenorrhea and pathologic changes which could become malignant. Such treatment can certainly not be considered truly conservative.





## Response of Varied Dermatoses To Piromen

*A pseudomonas polysaccharide, Piromen  
reportedly stimulates the reticulo-endothelial  
system and adrenal cortex when injected*

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This paper is a report on the use of Piromen,\* a pseudomonas polysaccharide, in 35 cases of varied dermatoses.

Piromen is a sterile nonprotein bacterial derivative of a pseudomonas species. It is nontoxic and nonanaphylactogenic and is prepared in colloidal dispersion for parenteral use.<sup>1</sup> The literature includes several reports on its use in treating allergies and dermatoses.<sup>2-8</sup> It is reported to stimulate the reticulo-endothelial system<sup>9</sup> and the adrenal cortex when injected.<sup>3, 9-11</sup>

### INTRODUCTION

The group studied was composed of 15 male and 20 female patients with an age range of from four months to 81 years. Twenty-six of the patients had had other therapy prior to Piromen. Prior treatment consisted principally of topical ointments, X-ray and antihistamines. Ten of the 26 had shown some im-

provement under prior therapy; 16 had shown no improvement.

Piromen was injected intravenously in 28 cases, intramuscularly in three cases, and subcutaneously in four cases. All intramuscular and subcutaneous injections were given to children under five years of age with one exception, a 20-year-old girl.

Dosage varied between 0.5 gamma (microgram) and 2.0 gamma per injection. Generally, one gamma was given for the first injection, although 0.5 gamma was used on several occasions and 2.0 gamma once. After the first injection the dosage usually was increased slightly to a level where a clinical response was noted and maintained there.

The dosage schedule was variable. In the majority of cases the patient was given an injection every three or four days until a clinical response was noted. The patient then was

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\*Travenol Laboratories, Inc., Morton Grove, Illinois.

FIGURE 1

Diagnosis	Total Cases	Cleared	Improved	Failed
Atopic Dermatitis .....	8		8	
Eczema .....	10	3	5	2
Urticaria .....	3	2	1	
Dermatitis Venenata .....	2	2		
Dermatitis Medicamentosa ...	1	1		
Totals .....	24	8	14	2

placed on a maintenance schedule of one injection every week, or in some cases every two weeks, the schedule being varied with the clinical demands. Duration of treatment was from one month to one and one-half years.

Eleven patients reported side effects from Piromen administration, 10 of them after intravenous administration. Six reported slight chills, three a feeling of fatigue, and one nervousness. A six-month-old infant with eczema suffered a slight chill after a 1.5 gamma subcutaneous injection. None of the reactions was serious or prolonged.

#### RESULTS

Results in 24 of the 35 cases are shown in Figure 1. The other 11 cases were dermatoses of unknown etiology which manifested themselves through rash, both generalized and localized, and itching. Of these 11 cases, eight improved and three cleared up after Piromen therapy.

Age did not seem to be a significant factor in the response to Piromen.

Sixteen of the patients (seven males and nine females) were under 21 years of age, 19 (eight males and 11 females) over 21. In the under-21 group five conditions (31.25%) cleared, 10 (62.5%) improved, and there was one failure. In the over-21 group, seven conditions (36.8%) cleared, 11 (57.9%) improved, and there was one failure.

There was no significant differences in response between men and women.

Of the 10 cases which had shown some improvement prior to Piromen therapy, eight showed further improvement after Piromen was used. Of the 16 cases which had shown no improvement under prior therapy, five conditions cleared and 11 improved after Piromen therapy was instituted.

#### CASE HISTORIES

A. K., aged 17, female. Diagnosis, severe atopic dermatitis. The patient had had this condition all her life and had received therapy of many kinds although she could not describe prior treatment specifically. She was placed on Piromen, one gamma intravenously weekly. Four weeks later the schedule was

1. Neswet, N. M., et al, *J. Am. Pharm. Assn.*, 39:456, 1950.
2. Kierland, R. R., Kulwin, M. H., *Arch. Dermatol.*, 62:571, 1950.
3. Randolph, R. G., Rollins, J. P., *Ann. Allergy*, 8:626, 1950.
4. Zindler, G. A. V., *Ann. Allergy*, 9:494, 1951.
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6. Samter, M., *J. of Allergy*, July, 1952.
7. McCorriston, L. R., *Canadian Med. Assn. Journ.*, Feb., 1953.
8. Guerrieri, J. A. V., *Clin. Med.*, 59:29-35, 1952.

9. Windle, W. F., et al, *Am. J. Med. Sci.*, 219:422, 1950.
10. Windle, W. F., et al, Changes in Endocrine Organs Induced by Bacterial Pyrogens, *Am. Physiol. Soc.*, (paper), Atlantic City, April 21, 1950.
11. Kirkendall, W. M., et al, *J. Lab & Clin. Med.*, 36:845, 1950.

changed to one gamma every two weeks. During this and subsequent periods she showed slow but steady improvement. Piromen therapy was discontinued after 6 months with the skin greatly improved but not entirely clear. She reports little or no itching.

D. K., aged 20, female. Diagnosis, chronic atopic dermatitis covering neck, face and arms. The condition had been present all her life and she indicated no prior therapy. She was placed on Piromen therapy, one gamma intramuscularly every three days. When she was first seen she was extremely tense and nervous. Phenobarbital was given concomitantly with Piromen. Therapy was discontinued after 5 weeks. Her skin was much improved and she reported she was being asked for dates. Her tenseness and nervousness were greatly reduced.

J. S., aged 4, male. He had been suffering from eczema for three to four months and treatment with thyroid (1/6 grain), and epsom salts baths brought no improvement. He was placed on Piromen therapy, 0.5 gamma subcutaneous injections every three days for nine days. He received an antihistamine drug and phenobarbital concomitantly. After nine days the dose was reduced to 0.5 gamma weekly and injections continued for 10 weeks. The skin was clear when treatment was discontinued.

P. A., aged 3, male. This child had suffered from chronic eczema since birth. Extensive use of topical applications had failed to improve his condition. He was placed on Piromen therapy, 1.0 gamma subcutaneous injections every four days. An

antihistamine drug, vitamin A and tar ointment were used concomitantly. After one month the dosage was raised to 1.5 gamma. No improvement was noted and treatment was discontinued after 11 weeks.

H. C., aged 55, female. Urticaria had been present for four to five weeks. Treatment with an antihistamine drug belladonna and phenobarbital had failed to improve her condition. She was placed on intravenous Piromen injections every three days. The first injection of 1.0 gamma produced a slight chill and the following two injections were reduced to 0.5 gamma. Some improvement was noted after the first injection and after three injections her skin was clear.

#### SUMMARY

1. Of 35 cases of various dermatologic conditions, 11 cleared up, 22 improved and two showed no improvement after Piromen therapy.
2. Of 10 cases which had shown some improvement on therapy prior to Piromen eight demonstrated additional improvement after Piromen therapy was begun.
3. Of 16 cases which had shown no improvement on therapy prior to Piromen, five cleared up and 11 improved after Piromen therapy was begun.
4. Slight reactions, primarily moderate chills were noted in 11 cases after injection of Piromen. None was serious or prolonged.
5. Age or sex had no apparent effect on response to Piromen.

12. Soylemezoglu, B., Wells, J. A., Studies on the Mechanism of the Leucocyte Response to Bacterial Pyrogen, *Am. Soc. Pharmacol. & Exptl. Ther.* (paper) Boston, Nov. 13, 1950.



## How to Treat Small Skin Tumors

*There is no single method for  
the proper treatment of all skin tumors—  
each problem must be individualized*

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In recent years there has been a growing tendency to consider most tumors of the skin as potentially malignant, to recommend—particularly true of the surgeon—that all skin tumors should be surgically excised. No doubt, this attitude has become more acceptable because of the uncertainty of most doctors as to the diagnosis and treatment of many cutaneous tumors. When not sure of the diagnosis, it is easy to cut it out and let the pathologist establish the diagnosis. When there is a legitimate doubt, there can be no quarrel with this attitude, but we should protest when this course is recommended for all skin growths. There is no single method for the proper treatment of all small skin tumors. A wide variety of measures can be successfully employed under the proper circumstances.

There are certain basic premises that must be assumed if this ap-

proach is accepted. First of all, the physician who treats such growths should be capable of clinically differentiating the common skin tumors. He must also recognize his limitations, since even the dermatologist of widest experience is sometimes in doubt and must enlist the assistance of the pathologist.

Secondly, he must have at his disposal, the personal techniques and physical equipment with which to handle the particular situation, be it surgical excision, electrosurgery or other destructive measures. In cases where x-ray therapy is indicated, the general practitioner should refer the patient to a colleague qualified to use it.

Thirdly, he should have the humility to accept the fact that there is no one way which is always best and be willing to individualize each problem.

It is not within the province of this presentation to discuss the dif-

LES  
ferential diagnosis of the common skin tumors. Any standard textbook on dermatology can be used as a guiding reference.

#### TREATMENT OF WARTS

Common warts are very commonly seen. Single warts, except on the sole of the foot, are best treated by electrodesiccation under local anesthesia. The current is held on until the lesion glows, after which the wart is snipped off with scissors, the base curetted and the spark reapplied to control bleeding. Plantar and periungual warts, except the mosaic variety, are better treated with x-rays, freezing with liquid oxygen or nitrogen, keratolytics, or by thorough curettage under novocain anesthesia, followed by the insertion of a piece of gel foam in the cavity. It is entirely possible to cure single or multiple warts with psychotherapy—a time-honored and legitimate form of treatment. Sel-dom, if ever, is it necessary to excise a wart except in cases of doubtful diagnosis. Multiple flat warts should not be removed with the electric needle because of scarring. Painting several times a day with full-strength Vlemincx' solution will usually melt them away without leaving scars.

#### SEBORRHEIC KERATOSES

Seborrheic keratoses are benign growths which are readily destroyed by superficial sparking with the electric needle followed by curettage. These growths need not be burned deeply. Senile keratoses, on the other hand, are premalignant lesions and must be thoroughly destroyed with the electric needle and the curet. Very early superficial ones may be readily cured by the application of a pencil of dry ice with moderate pressure for 10 to 15 seconds. Ordinarily it is not necessary

to cover the treated areas with a dressing.

Small sebaceous cysts are easily excised in toto, especially if they have never been infected. Where infection has occurred, the sac may be adherent and more difficult to remove. In such instances, or for that matter even in the uninfected cyst, other methods may be employed. With the electric needle inserted over the center of the cyst, a weak current is applied which creates an area of necrosis through which the entrapped sebaceous material may drain. The cyst will gradually shrink down leaving an insignificant scar. Another effective method is to incise and drain the cyst, following which a fragment of lunar caustic is inserted into the empty sac and a dressing applied. Three days later the coagulated sac may be lifted out.

#### CARCINOMAS

Basal-cell carcinomas should be individualized depending upon their size and location. Small ones may be thoroughly destroyed with the electric needle and curettage, while large ones are best treated by a qualified physician with x-ray therapy or radium. In areas such as the side of the neck surgical excision offers good cosmetic result.

Squamous-cell carcinomas on the extremities should be widely and deeply excised, and careful clinical examination made of regional lymph nodes, for evidence of metastases. On the face they are best removed by thorough electrical destruction if small, and by irradiation if large. In those persons with "farmers" skin, with excessive dryness and multiple lesions, it is probably best to avoid irradiation, since this aggravates the dryness with the possibility of causive new growths later in life.

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1. Sturnick, M. I., and Gargill, S. L.: Clinical Assay of a New Synthetic Estrogen: Vallestiril, *New England J. Med.* 247:829 (Nov. 27) 1952.



## "HAZARDS" OF NEVI

Perhaps the greatest confusion regarding skin tumors is in the group of nevi. More and more propaganda, emanating largely from the surgeons and oncologists, warns of the hazards of nevi, recommending that, since all nevi are potential malignant melanomas, the only safe way to treat them is to widely and deeply excise the lesion and surrounding skin. Nothing could be farther from the truth. All nevi are not potentially malignant and millions have been safely and satisfactorily removed by simply local destruction. It is true that the so-called junction nevus should be completely removed, and that when there is doubt about the exact type of nevus it is best to excise it. But this is the exception.

These statements are based upon a recent survey of treatment of over a million and a half nevi by over 200 experienced American dermatologists. Over 70% use non-surgical destruction, usually electrodesiccation, in at least 90% of the cases while only 7% employ surgical ex-

cision in at least 90% of the cases. Occasional mistakes are made, but the incidence is so low (0.0017%) as to show that qualified dermatologists have an excellent batting average. Individualizing each lesion permits safe removal without resorting to surgical excision and pathological examination of every nevus. The obviously benign cellular nevus may be effectively and safely removed by infiltrating the base with a local anesthetic solution, cutting off the tumor level with the skin with either a scalpel or scissors, and sparking or cauterizing the base. If there is reason for microscopic examination, the cut-off portion may be sent to the pathologist.

Too many physicians have been led to believe that melanomas and death can result from any mole. Such erroneous thinking had led to a great deal of needless surgery and unnecessary fear on the part of both the physician and the patient. It is time to reevaluate our thinking and accept the proposition that there is no one best method for handling all skin tumors.

## Effect of Butazolidine on the Excretion of Water and Electrolytes

On the basis of tests made on rheumatic patients and on healthy volunteers it appears that butazolidine (phenylbutazone) has a selective effect on the excretion of electrolytes and water, probably owing to increased reabsorption of sodium. The similarity to the action of salt-

conserving adrenal hormones is noted, and it is suggested that if edema occurs during treatment with phenylbutazone, the intake of sodium should be restricted and mercurial diuretics should be given a trial.

J. Green, P. O. Williams, *Lancet*, 1:575, 1953.



## Surgical Treatment of Intractable Pain

*Unless pain is truly intractable,  
surgical intervention for its symptomatic  
relief is never justifiable*

---

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The purpose of this paper is to consider the various types of intractable pain which may be relieved surgically and the procedures which may be employed for this relief. The paper is based on the author's personal experience although he owes much to his teachers and colleagues and lays no claim to originality.

In philosophical literature pain is considered to represent the frustration of desire, the opposite of pleasure which is the result of the satisfaction of desire. However, philosophers recognize two kinds of pain, the pain of sense, and the pain of loss or deprivation. It is the pain of sense that the physician is concerned with.

Pain is important as a warning of danger to the organism, but it is a distressing experience, and if long continued has a deleterious effect, not only upon personality and emo-

tional reactions but even upon vital organs.

Pain may be said to be intractable when it cannot be controlled by analgesic drugs and when its cause cannot be satisfactorily treated. This latter may be because the cause is not known as in the case of major neuralgia, or because it is not amenable to treatment as in advanced malignant disease. Unless pain is truly intractable surgical intervention for its symptomatic relief is never justified.

The threshold of pain is so variable that what one patient feels and describes as mild pain causes another to make bitter complaint. Again there is great variation in the emotional reaction of the individual to pain. Most individuals with low pain thresholds have a marked emotional reaction to pain with fear and anxiety, and these same individuals are usually intolerant of the

unavoidable sequelae of many of our surgical procedures on pain pathways.

#### MALIGNANT TUMORS

The most common cause of intractable pain that requires surgical treatment is inoperable malignant tumor and its metastases. Pelvic carcinoma is a great offender because it so frequently involves the lumbosacral pelvis. Carcinoma of the neck or throat also often produces intractable pain. All types of malignant tumors may on occasion produce intractable pain in some part of the body. Skeletal metastases are especially apt to be painful.

Angina pectoris is an example of pain that is important as a warning to the organism and frequently becomes so distressing as to seriously affect the patient's personality and emotions. Operative relief is demanded when the attacks are so frequent and severe as to incapacitate the patient and relief is not afforded by the usual vaso-dilator drugs.

#### SURGICAL RELIEF

Major causalgia is not frequent in civilian practice but is common in military service. It is the result of incomplete injury or irritation of major peripheral nerves, never occurring with complete section of nerves. When well established it is one of the most severe and persistent of pains and surgical relief is imperative.

Amputation-stump pain and phantom-limb pain are severe enough on occasion to warrant surgical treatment. Usually excision of peripheral neuromas will relieve the former but this procedure commonly fails in the latter. The mechanism of this latter pain is still unproven but is probably at the thalamic or even the cortical level.

#### MAJOR NEURALGIAS

Finally the major neuralgias frequently cause intractable pain that requires surgical intervention. These include trigeminal neuralgia, by far the most common, glossopharyngeal neuralgia and certain severe cases of occipital and intercostal neuralgia. Post-herpetic neuralgia is at times persistent and severe enough to require surgical intervention, but only after diagnostic nerve block indicates that surgery will relieve the pain.

In cases of malignant disease and occasionally in other conditions in elderly or debilitated patients, the life expectancy of the patient should warrant the procedure. These patients tend to die sooner than their physician anticipates, especially when subjected to surgery. The pain must be such that it cannot be made bearable by analgesics, or in the case of malignant disease, by controlled doses of narcotics.

#### CHRONIC INTRACTABLE PAIN

Patients with chronic intractable pain not due to malignant disease should never be allowed narcotics. Those who have malignant disease may, if their life expectancy is short, be allowed the use of narcotics in moderation. The pitfall in this method of management is the rapid increase of tolerance to the narcotic used and the necessity for increasingly larger doses if the pain is to be kept under control.

Finally, before subjecting a patient with pain to a surgical procedure, the surgeon should be reasonably sure that the procedure will relieve the pain. In the case of pain due to malignant disease it can usually be safely assumed that the organic part of the pain will be relieved by the appropriate surgical procedure, but anxious and fearful patients will still have their fears,

anxieties and emotional tensions. These may be increased as the patient realizes that his general physical condition continues to worsen even though his pain has been relieved.

#### RHIZOTOMY

The pain of trigeminal and glossopharyngeal neuralgia will be certainly relieved by rhizotomy, but in the case of trigeminal neuralgia the cutaneous anesthesia of the face and the paresthasias may be very distressing. In other types of intractable pain, especially causalgia, amputation-stump, or phantom-limb pain and post-herpetic pain certain surgical procedures do not always give relief, and pre-operative testing by procaine blocks of the nerve or nerves to be sectioned is essential to avoid disappointment to patient and surgeon. Even spinal anesthesia may be used as a pre-operative test where cordotomy is being considered for lower-extremity or lower-trunk pain. Although spinal anesthesia temporarily blocks all forms of sensation, and cordotomy is a selective surgical procedure with section only of the spino-thalamic tract, negative results are of importance. If spinal anesthesia produced to a level above the segments involved in the patient's pain does not relieve the pain, cordotomy will not relieve the pain and should not be undertaken.

#### DIAGNOSTIC BLOCK

When sympathectomy is considered for pain relief, diagnostic block of the portions of the sympathetic chain that it is proposed to remove should always be carried out, and if possible repeated more than once.

The variety of surgical procedures that can be used should be considered for each patient in the reverse order of their magnitude. This generally, but not always, corresponds to the reverse order of their level in

the nervous system. We may begin at the peripheral nerve level. Operative section or chemical block of peripheral spinal or cranial nerves outside the spinal canal or cranial cavity is a comparatively simple procedure, but it has many disadvantages and complications. It is not feasible for pain in the extremities because of the serious motor paralyses that result. It can be used for intercostal and for trigeminal neuralgia. Where the pain is self-limited and will not recur after regeneration, or where the life expectancy is short, peripheral nerve block or section of intercostal nerves or the branches of the trigeminal nerve is a satisfactory method of pain relief. Regeneration generally occurs in six to eight months and in trigeminal neuralgia the pain always recurs although not always as soon as nerve regeneration occurs.

#### SYMPATHECTOMY

Sympathectomy may produce pain relief by the improved circulation, this relief may follow removal of the sympathetic vasomotor fibers to a limb or organ. In other cases the relief is due to the section of visceral sensory fibers accompanying the portion of the sympathetic chain that is removed. Many disappointments have been recorded with attempts to relieve pain of various types and in various locations by sympathectomy. The pain of major causalgia can usually be relieved by sympathetic denervation of the affected limb. The procedure should not be considered unless repeated procaine blocks give temporary relief and fail to bring about permanent cure. Removal of the upper portion of the sympathetic chain including the rostral 2 or 3 thoracic sympathetic ganglia will relieve cardiac pain, especially that of angina pectoris. Operating on the left side only suffices, except in the rare cases where the pain radiates to the

right side only. In these cases it may be done on the right side. The stellate (cervico-dorsal) ganglion is usually spared in order to avoid a Horner's syndrome. Pre-operative procaine block should produce temporary pain relief before sympathectomy is considered. Paravertebral alcohol block of intercostal nerves requires a high degree of technical skill, and there is risk of certain complications, especially intercostal neuritis. Pain of bladder tumors, or of tuberculous or interstitial cystitis (Hunner's ulcer) may be relieved or greatly lessened by presacral neurectomy. This is a simple surgical procedure to a surgeon thoroughly familiar with the anatomic variations of the sympathetic fibers in this area. Pre-operative diagnostic procaine block of the presacral plexus is not technically feasible and the surgeon's judgment has to be the guide in evaluating patients for presacral neurectomy.

#### RETURN OF SYMPTOMS

In all sympathectomies regeneration tends to take place, with return of symptoms in many cases six to twenty-four months after operation. Fortunately, causalgia, once relieved, seldom recurs. Angina pectoris may recur if the patient lives long enough. In the author's experience with sympathectomy for interstitial and tuberculous cystitis a high percentage of recurrence of pain has taken place one or two years after operation.

Spinal subarachnoid injection of alcohol has been widely used for intractable pain in the lower extremities, by a few bold surgeons for pain at higher levels. Even with the most elaborate precautions it is a poorly controlled procedure, with a high incidence of motor paralysis or weakness and urinary and fecal incontinence. It should be reserved for patients with a short life expectancy with pain confined to the low-

er extremities. Preferably only one extremity should be involved and the patient should be already bedridden.

#### RHIZOTOMY

Rhizotomy of the dorsal roots of spinal nerves, the sensory root of the trigeminal nerve or the glossopharyngeal nerve gives permanent pain relief. Section of the sensory root of the trigeminal nerve by the temporal approach remains the most satisfactory method of relief of the agonizing pain of trigeminal neuralgia. It has a low operative mortality and the technic has been perfected by a large number of neurosurgeons. Intracranial section of the glossopharyngeal nerve by the suboccipital approach is specific for the rare glossopharyngeal neuralgia. In certain cases of intractable pain due to malignant disease either or both of these nerves may be sectioned. If it is necessary to cut both, it may be done through the suboccipital approach. If necessary to relieve pain in the neck as well, a hemilaminectomy with rhizotomy of the upper four posterior cervical roots may be added to the procedure.

#### CONSEQUENCE OF RHIZOTOMY

Rhizotomy has two disadvantages. If the pain is felt over a wide area the operative procedure becomes too extensive. Generally speaking, it is unwise to section more than four spinal nerve roots. The most serious consequence of rhizotomy is the permanent loss of all sensation in the distribution of the sectioned nerves. This makes the procedure unsuitable for use in the extremities unless the pain may be relieved by section of one or at most two roots. From section of more roots the resultant loss of position sense (muscle and joint) will be too disabling. Further the loss of light touch produces troublesome paresthesias in many patients. The persistent com-

plaints of patients who have had trigeminal root section has led to repeated and continuing attempts by neurologic surgeons to find a procedure that would relieve the pain without causing complete permanent anesthesia of the face. It appears that the loss of light touch is responsible for the often bitter complaints of these patients as those who have had section of the spinothalamic tracts alone (cordotomy or medullary tractotomy) seldom complain of paresthesias to the degree that patients with rhizotomies do.

#### CORDOTOMY

Cordotomy is the procedure of choice where life expectancy warrants it for intractable pain of the lower extremities or pelvis and abdomen. If the pain is bilateral the procedure should be carried out in two stages, at least five days apart and with the cord incisions at least two spinal segments apart. With this precaution the complications of motor paralysis and bladder and bowel incontinence can be largely avoided. The procedure is best performed under local anesthesia so that the desired level of loss of sensation can be verified before the wound is closed. The operation is most conveniently done between the fifth and seventh thoracic segments. It should seldom be attempted at a lower level as spino-thalamic tract section in the lower thoracic cord will not relieve deep or visceral pain from the pelvis. In cases of pain not due to malignancy, and especially in cases of amputation-stump or phantom-limb pain, spinal anesthesia should be used as a pre-operative test. Unless an adequate spinal anesthesia relieves the pain for the duration of the anesthetic, cordotomy should not be carried out in that case.

Intractable pain in the chest or upper extremity can be relieved either by high cervical cordotomy

or medullary tractotomy. In the latter procedure the spino-thalamic tract is sectioned at the lower end of the medulla. This operation is more formidable than thoracic cordotomy but not more so than cervical cordotomy. While some surgeons prefer high cervical cordotomy, other including myself find medullary tractotomy easier and safer. Both of these procedures have a prohibitively high risk if bilateral. While successful bilateral two-stage procedures have been reported, most surgeons will do well to avoid the bilateral operation. Obviously, spinal anesthesia cannot be used as a pre-operative diagnostic test for pain involving the chest or upper extremity. The judgment of the surgeon has to be the guide in evaluating the suitability of the patient for this procedure. Involvement of the brachial plexus by spread of carcinoma of the breast or from the apex of the lung (Pancoast or superior-sulcus tumor) is the most frequent indication for high cervical cordotomy or medullary tractotomy. Selected cases of phantom-limb or amputation-stump pain in the upper extremity may also be relieved by medullary tractotomy. Mesencephalic tractotomy, section of the spino-thalamic tract at the mid-brain level, is another intracranial procedure of magnitude, popular with a few surgeons. The author has no personal experience with it.

#### THALAMOTOMY

Thalamotomy, or the production of controlled electro-surgical lesions in the thalamus by means of some modification of the Horsley-Clarke stereotaxic apparatus, is a promising method, yet in the experimental stage, of attack on intractable pain.

#### LOBOTOMY

Prefrontal lobotomy offers a valuable method of relief of intractable

pain in certain cases. It does not interrupt any primary pain-pathway or destroy any center of pain perception. Its success depends upon its effect upon the patient's personality and emotional reactions as a whole. It relieves anxiety and emotional tension caused by pain but does not destroy the ability to perceive and recognize pain. Patients after prefrontal lobotomy do not have their former fear or anxiety about pain. They frequently do not complain of pain or ask for medication to relieve pain, but when questioned they admit having pain and may insist that it is as bad as before lobotomy. The dulling of intellect and the blunting of emotional reaction are the greatest disadvantages of prefrontal lobotomy. Many families find it difficult to accept the changes in the patient's personality and attitude and it is very important to be sure that the family appreciates and understands the probable effects of lobotomy before it is carried out.

Some surgeons have reported excellent relief of pain with unilateral lobotomy which produces little if any effect on personality and intellect. In my experience the bilateral procedure has generally been necessary. However, I believe that in cases of intractable pain prefrontal lobotomy should be planned in two stages, with omission of the second stage if the first proves adequate.

Success in the treatment of intractable pain can only be achieved by careful individual evaluation at the nature of the lesion or syndrome causing the pain, the location of the pain, the pain threshold, and the

emotional reaction to the pain and its cause. The procedure to be used must be chosen with all these factors in mind. Where feasible preoperative procaine blocks or spinal anesthesia should indicate that pain relief will follow the intended surgical procedure. Insofar as possible, the entire situation including the immediate surgical risk and the sequelae to be expected should be discussed with the patient as well as the family. Once the procedure has been carried out a confident and firm but sympathetic attitude on the part of both physician and surgeon is of great importance. Too often the doubts and misgivings of his doctors are all too apparent to the patient and add to his fear and anxiety.

#### SUMMARY

The principal causes of intractable pain that requires surgical treatment are inoperable malignant disease, major neuralgia, major causalgia, angina pectoris, and amputation-stump and phantom-limb pain. The surgical methods used to relieve pain are in the order of their ascending levels in the nervous system; peripheral nerve block or resection, sympathetic block or resection, rhizotomy of dorsal or sensory nerve roots, cordotomy, medullary tractotomy, thalamotomy, and prefrontal lobotomy. The advantages of these procedures and their indications and contraindications have been reviewed. Complete evaluation of the individual patient with intractable pain is necessary before a satisfactory surgical procedure for his relief can be determined.





## CURRENT LITERATURE

### Treatment of Malignant Disease with Radioactive Isotopes

*The application of radio-isotopes as substitutes for radium and x-ray therapy offer practical advantages*

---

G. W. BLOMFIELD, M.D., *Medical Director, Sheffield National Center for Radiotherapy, University of Scheffield, England*

The therapeutic use of radio-isotopes depends upon the biological effects of the radiation emitted. Radio-gold, in the form of a radioactive colloid solution, for example, can be used in the treatment of malignant pleural or peritoneal effusions by virtue of the beta radiation emitted and, wherever the colloid is in contact with the tissues, the biological effect will be maximal.

Thyrotoxicosis can be effectively treated with radioactive iodine however severe the disease may be. Here a high proportion of the radio-iodine is taken up by the gland, where it gives off its beta and gamma radiations without affecting the skin or the trachea, the dose being almost entirely limited to the gland.

Contraindications to its application are pregnancy and the presence of a large toxic adenoma. It does not replace surgery. In fact, less than 10 per cent of thyroid carcinomas are suitable for radio-iodine therapy. For such therapy to be effective the tumor must concentrate iodine and must therefore be a functioning growth. The best response is obtained in follicular and alveolar carcinoma. Papillary carcinomas show but little tendency to concentrate iodine and anaplastic growths show no effective concentration. The so-called "aberrant" thyroid in the neck, associated with a malignant gland, shows the best response of all.

For the effective local irradiation

of carcinoma of the bladder, three new methods are available: (1) intravesical use of radioactive isotopes in solution (most suitably bromine,  $\text{Br}^{82}$ ); (2) use of a very high intensity source of radioactive cobalt, placed centrally in the bladder, and (3) implantation of radioactive tantalum wire which gives off gamma radiation almost identical with radium.

Radioactive gold colloid in a solution of gelatin has been used with success in the palliation of malignant effusions. The gold ( $\text{Au}^{198}$ )

gives off beta and gamma radiation, but it is the beta radiation which accounts for most of the irradiated energy. Considerable success has been reported in the palliation, by this method, of malignant effusions.

The basic principles of radiotherapy remain, of course, quite unaltered by the application of radio-isotopes as substitutes for radium and x-ray therapy; they do provide, however, convenient or more powerful sources of radiation which offer certain practical advantages.

*Postgrad. Med. J.*, 29:505, 1953.



### Polymyxin-Bacitracin Ointment in Dermatology

Polymyxin B is a stable polypeptide with marked bactericidal action against many gram-negative bacilli and especially against *Pseudomonas aeruginosa*. Variants of polymyxin have been announced independently by three groups of investigators. These variants, designated as A, B, C, D, and E, have similar antibacterial spectra but differ in their amino-acid components and toxicity.

In this study the results are reported of the topical application, in an ointment base, of polymyxin B combined with bacitracin. The combination consisted of 10,000 units of polymyxin B and 500 units of bacitracin per gram of a petrolatum base with a specially low melting point. The ointment was used for the treatment of a variety of infected primary and secondary dermatoses in 429 patients. In most cases, blephari-

tis marginalis appeared to respond extremely well to the preparation. A good response to the ointment was also observed in a large series of infectious eczematoid dermatitis. A few instances of irritation were observed which usually could be traced as due to the bacitracin component. The overgrowth of *Pseudomonas* or *Proteus* organisms which is a common finding with other antibiotics, and especially with penicillin, is almost entirely avoided by the use of polymyxin.

It is concluded, in short, that the results of this study warrant the general use of this preparation for the treatment of primary and secondary infections, and prophylactically after such procedures as fulguration, irradiation and cryotherapy.

R. L. Kile, et al, *Arch. Derm. & Syph.*, 68:296, 1953.



## An Evaluation of Phenylbutazone

*This new drug affords relief from pain in the majority of patients suffering from rheumatic disease—minimum dosage is essential*

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This new antirheumatic drug has been the subject of considerable controversy principally because of its possibility to produce serious side effects in some patients, although in most instances these effects are of minor import and are rapidly reversible. Most observers are agreed that the drug affords relief from pain in a majority of patients with rheumatic diseases, and that, to a lesser extent, it decreases swelling and increases the mobility of the affected joints. The relief usually sets in within two or three days after administration of the drug is begun, and the effect is completely dissipated within seven to ten days after discontinuance of the therapy. It must be kept in mind that phenylbutazone, like the steroids, has no curative properties.

The most dramatic response obtained by the drug is in acute *gout*. Here it brings about prompt relief

in 80 to 85 per cent of the patients, and sometimes complete remissions within 24 to 48 hours. It is also very effective in relieving the pain of non-articular rheumatism, such as "painful shoulder" and bursitis, but remissions may not be as complete or lasting as in *gout*. In rheumatoid arthritis, 50 to 80 per cent of the patients obtain varying degrees of subjective relief from pain. The drug seems to be somewhat more effective in the spondylitic than in the peripheral type of the disease. The drug is not advised for the relief of symptoms of degenerative arthritis because of the age of these patients.

Toxic reactions are experienced by some 25 per cent of the patients, but discontinuance of the drug therapy is necessary in only about 10 per cent of the cases. The most common reactions are gastrointestinal upset, edema and rash. Less common are generalized allergic re-

actions with stomatitis, purpura, hematuria and agranulocytosis. However, several patients have died of agranulocytosis. Reactivation of quiescent ulcers and unexplained gastrointestinal bleeding have been reported. The drug is thus potentially dangerous and must be handled as such.

Dosage must obviously be kept at a minimum and should never exceed 800 mg. daily. It should be tak-

en with food, or with an anti-acid preparation that contains no sodium. If the patient is given adequate amounts of phenylbutazone but experiences no relief within 4 to 7 days, administration of the drug should be discontinued. The blood must be examined before the drug therapy is commenced and frequently and regularly during treatment.

*Calif. Med.*, 79:211, 1953.



### **Antibiotic Resistance of Pathogenic Staphylococci**

The resistance of some 500 strains of staphylococci against currently used antibiotics was evaluated. Of the strains examined, 185 were from the respiratory tract, 124 from the skin, 57 from abscesses, 41 from cases of osteomyelitis, 35 from the urine, 33 from the feces, and 25 from the blood. The sensitivity of these strains was determined by a serial two-fold agarplate dilution method, and tests for penicillinase production were carried out.

The results of the tests made with 9 antibiotics indicated a wide range for penicillin, aureomycin and terramycin. Distribution curves for streptomycin, neomycin, chloramphenicol, and polymyxin B showed less variation and, especially erythromycin, no naturally occurring staphylococci of high or moderate resistance were encountered. Similar results have recently been reported for carbomycin.

Weight for weight, the order of effectiveness was: erythromycin, aureomycin, terramycin, bacitracin,

streptomycin, chloramphenicol, neomycin, polymyxin B, and penicillin, but about 20 per cent of the strains were more sensitive to penicillin than the rest. Of the strains tested, 25% were sensitive to penicillin, 2% were intermediate in resistance, and the rest resistant; 66% were sensitive to aureomycin and 33% resistant; the majority, however, were intermediate in their sensitivity to chloramphenicol.

Ability of the strains to produce penicillinase exhibited a striking relation to their susceptibility to penicillin. No direct correlation was found between degree of sensitivity to any of the antibiotics and the source of the staphylococci. No penicillin resistant strain was resistant to aureomycin or terramycin, but all strains resistant to these two antibiotics were resistant to penicillin. On the other hand, the majority of the penicillin-resistant strains were sensitive to aureomycin or terramycin.

M. Finland, T. H. Haight, *Arch. Int. Med.*, 91:143,

## Value of Frozen Sections in Diagnosis

*With the advent of needle biopsy, rapid freezing and pathologic examination of the cores, an almost immediate diagnosis is possible*

---

M. B. DOCKERTY, M.D., Rochester, Minnesota

Both the general practitioner as well as the surgeon and their respective pathologists should know the possibilities offered by the use of fresh frozen sections as a means of rapid diagnosis. Some of the significant information which frozen sections can supply is here briefly enumerated. The first question which naturally arises is whether a specimen for biopsy is representative of the live tissue. The answer is that even poorly prepared "slabs" are thin enough to allow for a decision as to the tissue being alive or dead. Nonviable tissue rarely discloses useful information after treatment by any method of fixation, and sectioning and its identification as such demands further sampling for biopsy. The answer to the question whether a lesion is benign or malignant often determines the type of operation to be done. In more than 95 per cent of cases, this problem is settled immediately at the freezing

microtome. Malignant changes in such locations as the uterine cervix or fundus, the bladder, the breast, the thyroid, the brain and in bone—to list a few—are delineated just as clearly by the rapid freezing method as by routine paraffin techniques carried out several days later. When the lesion is a "debatable" one, it is always possible to withhold opinion and "stall for time with hematoxylin and eosin." Such lesions will frequently still be "debatable" after prolonged fixation, embedding and staining.

A good example of resolving the diagnostic dilemma of whether a lesion is inflammatory or neoplastic is afforded by the thickened pancreatic head in a case of obstructive jaundice. This dilemma can be resolved rapidly by use of the Silverman needle to secure deep cores of tissue. Microscopic examination of these fragments can be carried out by freezing almost as rapidly as the

surgeon can remove them.

Needle biopsy is coming into its own, especially for the general practitioner. Tissues so secured from the breast, prostate gland, thyroid, lymph nodes, spleen and liver all lend themselves to examination by the rapid freezing method. Consider the patient whose nodular liver possibly contains metastatic tumors. The clinician weighs the appreciable risk of exploratory laparotomy against the usefulness of information obtained thereby. However, with minimal risk, multiple sampling of these nodules can be done by means of the Silverman needle. Pathologic

examination of these cores of tissue often settles a diagnosis that otherwise would require a week's hospitalization.

Finally, the method directs approaches to bacteriologic investigation. Many infections, particularly granulomas, require specific antibiotic therapy based on isolation of the causative organism. Use of fresh frozen sections may allow identification of the specific nature of these lesions. Paraffin blocks, on the other hand, make poor material for bacteriologic investigation.

Minnesota Med., 36:387-388, April, 1953.



### Treatment of Urinary Tract Infections With Nitrofurantoin

This new chemotherapeutic drug, "furadantin" (nitrofurantoin; N-(5 nitro-2-furfurylidene) -1-amino-hydantoin), was given an experimental trial at the Cook County Hospital, Chicago. It is pointed out that the nitrofurans, in general, offer stability, a wide antibacterial spectrum, and little tendency to the development of bacterial resistance. They found that absorption of the drug following oral administration was practically complete: about 45% was excreted in the urine, but the blood levels were extremely low. A state of stable supersaturation can exist in the urine, and this suggests that crystalluria need not be feared. The antibiotic is effective against many gram-negative and gram-positive bacteria and certain protozoa *in vitro* and *in vivo*. It is not effective,

however, against rickettsia, viruses, or fungi *in vitro*. Combination of furadantin with penicillin or streptomycin has definite synergistic effect *in vitro*.

With the recommended dosage of 5 to 7 mg/kg of body weight, nausea occurred in only 2 of 59 patients. On a higher dosage of 10 to 12 mg/kg of body weight, 6 of 25 subjects had nausea and one vomited.

Furadantin was administered to 12 patients with urinary infections who had previously been unsuccessfully treated with sulphonamides, penicillin, and streptomycin; good results were obtained in 8 of these patients. The authors conclude that this drug appears to offer much promise in the treatment of bacterial urinary infection.

S. Mintzer, et al, *Antibiot & Chemother.*, 3:151, 1953.

## Management of Diabetic Acidosis in Children

*Ketonemia and acidosis are primarily due to insulin insufficiency rather than to over-ingestion of carbohydrates*

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G. M. GUEST, M.D., *Children's Hospital Research Foundation and Department Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio*

Theoretically, the diabetic patient should never go into ketonemia, acidosis and coma, if he is under proper management. Ketonemia and acidosis are primarily due to insulin insufficiency rather than to over-ingestion of carbohydrates. With lack of insulin there is impaired glycogenesis and loss of glycogen from the liver. The liver cells burn more fat, leading to overproduction of ketone bodies and production of ketone acids, resulting in decreased alkaline reserve, decreased bicarbonate in the blood plasma, and lowered pH. The state of acidosis, per se, leads to increased catabolism, liberation from the cells of labile intracellular constituents into the plasma, which are lost into the urine. The increased urinary excretion of phosphates, potassium and sodium, leads to increasing acidosis, inability of the body to retain water, and aggravation of the progressively de-

veloping state of dehydration. Dehydration itself is an important factor in the development of acidosis. The loss of electrolytes aggravated by the state of acidosis is a principal factor in development of dehydration, the additional factor being diuresis. The factor most closely associated with mortality has been shown to be not hyperglycemia or severity of ketosis, but the degree of acidosis, as measured by low pH and the length of time it has been low. With long continued acidosis there is an element of irreversible tissue change.

Recovery is dependent upon rehydration, effective insulin action and the attendant anabolic effects of insulin; administration of parenteral fluids (salt solution, alkalies, glucose); supportive treatment by chemotherapy in the presence of infection, vitamins during the recovery period, and oral fluids. Glucose,

and especially hypertonic glucose solution, should *not* be given until insulin action becomes effective.

The sequence of therapy is, first, insulin in appropriate doses, preferably small, repeated doses rather than initial large doses of several hundred units. There is evidence that insulin may be destroyed in the acidotic patient, or excreted; thus repeated small doses give the promise of more effective continuous action. Next is the administration of salt solution in appropriate amounts to improve the circulation. Then the administration of alkalis to bring the pH of the blood to normal and, after the third or fourth hour, the

administration of glucose in 5% or even 10% solution, to accelerate glycogenesis.

Most importance attached to the role played by potassium in the post-acidotic period. The great question is the size of the dose to be given. The amount must depend on the ability of the tissues to absorb it, and the state of the patient with regard to previous depletion. Much research remains to be done on the indices which govern a rational plan of potassium dosage. In the meantime it will be best to give minimal amounts, with careful observation of the electro-cardiographic findings.

*Proc. Institute Med. of Chicago, 19:267, 1953.*



### **Action of Roniacol in Peripheral Vascular Disorders**

Roniacol was administered to 40 patients, 23 of whom were suffering from various peripheral vascular disorders, the remaining 17 being normal controls. The drug was given by mouth in doses of 25 to 100 mg., or by intravenous, intramuscular, or intra-arterial injections in doses of 100 mg (occasionally 200 mg intramuscularly). The drug was well tolerated by all the routes. The following circulatory effects were observed after its administration: (1) a slight fall in the pulse rate; (2) a slight fall in both systolic and diastolic blood pressure in most cases, including some hypertensive subjects; (3) a fall of 0.1° to 0.9° C. in the oral temperature; (4) a rise of 1° to 5° C. in the cutaneous tem-

perature in the great majority of cases; (5) a slight increase in the functional capacity of the legs, as measured by ergometry, in 6 out of 8 cases tested; and (6), intense congestion of the retinal arterioles in all subjects examined.

It is concluded that roniacol dilates small arteries and arterioles, but has no or little effect on the large arteries. It is effective by whatever route of administration is employed, although oral administration gives the most constant results. The drug should be useful in the treatment of peripheral arterial disease when improvement of the collateral circulation is desirable.

*C. M. Castro, L. De Soldati, Angiology, 4:165, 1953.*

## CASE REPORT

### Case Record of the Massachusetts General Hospital

Dr. Marshall K. Bartlett: A nulliparous woman of 20 was staining by vagina at the time that her period was due, had symptoms and signs of some acute process in the lower abdomen and had a positive Aschheim-Zondek test. I assume she was pregnant. Was the complication related to the pregnancy?

There was a great many things against appendicitis. The pain started in the lower abdomen. There was intermittent pain in the r.u. qu. which does not help much one way or the other. But from then on the signs on examination seem to have pointed to something in the pelvis. She had exquisite tenderness on movement of the cervix on the initial examination and, 48 hours later, a definite mass behind the cervix. She had minimal GI symptoms and no nausea or vomiting, which is again more in favor of a lesion in the pelvis than of appendicitis.

Could this have been pelvic inflammatory disease? That is an unusual complication of early pregnancy. There was no substantial fever at any time and no chills, and

the process subsided rather promptly during the first admission. It seems unlikely that that picture represented pelvic inflammatory disease from infection in the tubes.

An ovarian cyst is a common cause of acute abdominal emergencies in pregnancy, but it fails to explain certain things in this history. The pelvic findings were variable: at first there was a thickening and then a mass behind the cervix; both were more on the left in the first admission; there were findings on the right, and no definite mass on the second admission. I should consider an ovarian cyst more seriously if the mass had been more definite and more consistent. If there was an ovarian cyst, there must have been some interference with its blood supply, or hemorrhage into it, to account for the acute symptoms. That would not account for the vaginal bleeding. A patient in early pregnancy with a twisted cyst does not have any particular reason for staining by vagina. The fall in hgb. from 15 to 12.5 gm. in 48 h. should not be overlooked.



Endometrial cysts that rupture are seen occasionally during pregnancy. I do not see how that could account for the vaginal staining and the fall in the hgb. which I think must have represented a fair amount of blood loss.

Among the conditions related to pregnancy, which ones could explain this picture? As far as I know, only twice have we seen bleeding from the corpus luteum of pregnancy; each patient 6 weeks pregnant.

Ectopic pregnancy explains the symptoms and signs that we are given here more fully than anything else, although it was a little early for vaginal bleeding from an ectopic pregnancy. The Aschheim-Zondek test tells us only that there is a living ovum in contact with the maternal circulation and so does not rule

out an ectopic pregnancy. The initial episode quieted down in the hospital on bed rest, with cessation of the abdominal pain and the vaginal staining. When the patient returned home the staining started again; she therefore came back. After she had been in the hospital 48 h. abdominal pain began, more severe and with more tenderness, spasm and decreased peristalsis, and a fairly substantial fall in the hgb. acute tenderness on movement of the cervix and fullness in the vault.

#### *Dr. Bartlett's Diagnosis*

Ruptured tubal pregnancy.

#### *Anatomical Diagnosis*

Ruptured tubal pregnancy.

At operation, there was 500 c.c. of blood in the abdominal cavity.

*The New England Journal of Medicine*, Nov. 12, 1953, with permission of the Editor.



### **Smoking and Carcinoma of the Lung**

This study consisted in a comparison of smoking histories obtained retrospectively from patients suffering from cancer and from other diseases. The data were collected during the period 1938-43 by personnel of the U.S. National Cancer Institute from patients attending hospitals in 4 different cities. Information was obtained on a variety of subjects, including smoking, from some 2847 white male patients. In 242 instances the smoking history was inadequate; 615 patients were not suffering from cancer. The site of the cancer in the remaining patients was as follows: lip, 571; tongue, 132; other parts of the buccal cavity, 348; pharynx, 85; esophagus, 104; larynx, 273; and lung, 477.

The results show close correlation

between the number of cigarettes smoked and the prevalence of cancer of the lung, and between the amount of tobacco smoked in pipes and the prevalence of cancer of the lip and of the buccal cavity other than the tongue. Less distinct relations are apparent between laryngeal cancer and cigarette smoking and between cancer of the tongue and pipe smoking. The evidence with regard to esophageal cancer is indefinite and is clearly lacking with respect to pharyngeal cancer. The data are insufficient for conclusions to be drawn in regard to cigar smoking. The authors conclude that "the etiological significance of these associations remains unestablished."

D. A. Sadowsky, et al, *J. Nat. Cancer Inst.*, 13:1237, 1953.

## AIDS IN DIAGNOSIS

### The Present Status of Liver Function Tests

The tests which assist in differentiating medical and surgical jaundice are those which are concerned with parenchymal damage. These include the cholesterol partition, alkaline phosphatase, the plasma protein fractions and the serodiagnostic tests based on them. It is worthy of comment that the BSP test assists materially in the diagnosis of liver damage especially when jaundice is inconspicuous. A marked grade of BSP retention under these circumstances is highly suggestive of marked liver damage or circulatory impairment. Prolonged and complicated biliary obstruction introduces disturbing elements in diagnosis. Here the observation and interpretation of clinical events are decisive in the final analysis.

The liver function tests are as indispensable for adequate management of patients with hepatobiliary disease as they are for diagnosis. This adds considerably to the cost of treatment since the tests require skilled technicians and fully equipped laboratories. The icterus index cannot replace the determination of the bilirubin fractions. Icterus index has no further place as a test of liver function in a modern hospital or laboratory. The flocculation and turbidity tests cannot be employed in place of the serum protein fraction determinations. The

flocculation and turbidity reactions are being used incorrectly as the sole laboratory guide by some in the diagnosis and management of patients with liver disease.

The liver function tests also play an indispensable role in screening industrial applicants, blood donors for subclinical liver disease, and in evaluating the toxicity of pharmaceutical agents before clinical release.

S. S. Lichtman, *Rev. Gastroenterology*, April, 1953.

### Diagnosis and Treatment of Achlorhydria

One hundred patients with oral medical complaints were investigated, and of these 28 showed achlorhydria. The author has found that certain atrophic and irritative conditions of the oral mucosa which do not completely respond to vitamin therapy may be correlated with achlorhydria.

In the present investigation, all cases of oral inflammation were subjected to estimation of gastric acidity. The method employed involved the administration of a cation - exchange-indicator quinine by mouth and the subsequent determination of urinary quinine. This simple procedure was acceptable to all patients and obviated the need for a stomach tube.

Hydrochloric acid cannot be given by mouth in adequate dosage. In this

series a new preparation was used, consisting of betaine hydrochloride 440 mg., contained in a coated tablet and marketed under the trade name of "Normacid." Release of acid in the stomach is slow, as was confirmed by x-ray and gastric analysis. The recommended dosage is one tablet before meals for one month, after which it may be increased to two tablets. The therapy has proved effective in the relief of oral symptoms and in curing superficial inflammation and atrophy in a large proportion of cases.

G. S. Sharp, *West. J. Surgery*, 61:353, 1953.

### The Electrogastrograph

Electrical potentials generated by gastric function may be detected by means of a small silver-chloride electrode in the stomach and an electrode on the skin. The potentials are amplified and recorded by an instrument named "electrogastrograph." Two types of electrical changes are found: (1) a steady potential difference due probably to the secretory activity of the cells of the gastric mucosa and varying, in a series of normal subjects, between -10 mV. and -25 mV. (average -15 mV.); (2) smaller alternating waves due to muscular activity, which consists of a basic pattern of slow waves (3 per minute) on which are superimposed smaller waves of higher frequency.

In 20 patients with duodenal ulcer, the steady potential difference was found to average +10 mV., and the smaller alternating waves were increased in amplitude and frequency. One supposedly healthy control subject was found to have a high potential, and 6 months later developed a duodenal ulcer which was diagnosed radiologically. Acute gastric erosions gave a similar electrogastrogenic picture to that of duodenal ulcer.

Recordings of low activity with

irregular spikes of potential were found in patients with carcinoma of the stomach, but as yet no specific pattern has been identified. Certain drugs have a constant effect; histamine (0.25 mg.) caused a rise of 5 mV., and atropine and "banthine" caused a depression of potential and a slowing of the wave pattern. Banthine given therapeutically for duodenal ulcer reduces the potential to within normal limits.

H. S. Morton, W. W. Martin, *Rev. Gastroenterology*, 20:37, 1953.

### Iron Metabolism

A new technique is described which is said to make it possible to assess the need for iron therapy in patients. The method is particularly useful in the anemia of infection, which is often associated with a low serum iron level, but in which there are ample iron reserves, thus making treatment with iron compounds unnecessary.

The method was applied to some 298 patients in whom assessment was made of the hemosiderin contained in the sternal marrow, followed by an evaluation of its significance. The specimen, obtained in the usual manner, was mixed with sodium citrate, and smears were made from marrow particles. The hemosiderin granules could be seen without staining under an oil-immersion lens, and with practice it was unnecessary to employ a special stain. It was found that the amount of hemosiderin in the marrow of women was less than that in the marrow of men in conditions except iron-deficiency anemia. In the latter condition, that is, in iron deficiency anemia, it was generally absent in both sexes. Estimation of iron content should therefore be made an essential part of the bone marrow examination.

A. R. Stevens, et al, *Ann. Int. Med.*, 38:199, 1953.

## THERAPEUTIC TRENDS

### Sodium Salicylate in Treatment of Gout

Satisfactory results are reported from the use of sodium salicylate in the treatment of chronic gout. The total daily dosage varied from 60 to 140 grains given in three divided doses spread equally through the 24-hours. It was dispensed in a fluid mixture containing an equal quantity of sodium bicarbonate, a flavoring agent, and sodium sulfite as a preservative.

Among the 29 patients who received salicylate treatment for periods of up to 34 months, there were only two in whom such treatment did not control the serum uric-acid level—one was a patient with severe renal disease; the other was a defaulter.

Considerable improvement occurred in all patients during the periods in which sodium salicylate maintained the serum uric at normal or nearly normal levels. In 20 patients, pain and stiffness of the joints disappeared. Tophi were noticed to disappear, ulcers to heal, joint destruction to be arrested, and the range of movements to be increased.

Side effects were minimal; in only 2 cases had treatment to be stopped. Tolerance to the drug usually developed within a few weeks. In no case did hemorrhage occur, but hypoprothrombinemia was not uncommon. When the prothrombin con-

centration fell below 25 per cent of normal, oral vitamin K, 10 mg twice daily, was given until a normal value was obtained. It is considered that there is no justification for dietetic restriction. For acute gout, colchicine is the drug of choice. The pharmacological action of sodium salicylate is dependent upon its capacity to block tubular reabsorption of uric acid.

F. G. W. Marson, *Quart. J. Med.*, 22:331, 1953.

### Dietary Treatment of Hypertension

The practical choice lies between the rice diet and other diets of low sodium content (less than 200 mg. per day). Extradietary sources of sodium (stomach powders, water-softeners) should be avoided; salt substitutes are unsatisfactory and, in the case of lithium chloride, dangerous.

Cation-exchange resins are less satisfactory in the treatment of hypertension than in that of congestive heart failure or nephrotic syndrome. Low-sodium diet can with advantage be combined with hexamethonium therapy. In malignant hypertension speedier measures than sodium restriction are, as a rule, needed.

I. H. Page, A. C. Corcoran, *J. Clin. Nutr.*, 1:7, 1952.

### One-Dose Prophylaxis and Three-Day Cure of Gonorrhea

On the basis of the total experience, the current recovery rate from gonorrhea treated with penicillin is 90%. In the remaining 10% the reason may be interference with free drainage of the infection, as in those with small urethral strictures, prostatitis, periurethritis, and the like. In this type of complication, surgical intervention is helpful.

Many of the resistant cases turn out to be due to other organisms or concomitant infections with trichomonas, diphtheroid, pleural pneumonia-like organisms, staphylococci, and a variety of others.

A report on 216 soldiers with "penicillin-resistant" infection, smear and culture showed gonococci in only 9% of the cases. In those 9% adequate penicillin brought a cure in 3 days.

Not only the urethritis, but the prostatitis and the gonococcal ophthalmia respond to penicillin therapy, provided drainage is free. Lack of free drainage may account for gonorrhea in females being more resistant, disease in the deep glands of the cervix, Bartholin's glands, tubes, and ovaries. The female requires a great deal more penicillin and more prolonged treatment to bring about a cure of gonorrhea.

300,000 units aqueous procaine penicillin daily for 3 successive days eliminates the gonococci from the smears in 100% of the cases, and brings about the complete clinical cures in at least 90%. The criteria for clinical cure call for the disappearance of discharge, and smears and cultures negative for gonococci for three weeks following treatment. The 5 to 10% of the cases in which discharge persists fail to show gonococci in the cultures of the discharge, and the remaining infection in these cases is due to other organisms.

The prophylactic method of choice is the use of a tablet of 250,000 units of penicillin taken promptly after exposure.

In treating patients for gonorrhea one has to consider the possibility of masking concomitant syphilis. A blood serologic test for syphilis should be made every 2 weeks for at least 3 months.

*New York State Jour. of Med.*, 53:1564, 1953.

### Isoniazid and Tuberculosis

The Committee on Therapy of the American Trudeau Society has released the following directions respecting the use of isoniazid. "Patients should not be treated with isoniazid alone. Further studies are needed to determine which combination of drugs will be most effective. In the meantime, if isoniazid is used streptomycin or PAS or both should be given concurrently."

Emphasis is laid upon the frequency of toxic effects on the central nervous system, which range from simple hyperreflexia to acute psychoses of the manic type, and are more likely to occur in patients with previous cerebral disease and idiopathic epilepsy. Allergic reactions have been recorded including dermatitis, purpura, arthralgia and asthma. Albuminuria and microhematuria have been "common but not serious." Hepatic damage has been reported in a few instances but "no serious blood dyscrasia has yet been reported." The report concludes: "In view of the toxicity of isoniazid and the uncertainty about the control of isoniazid-resistant strains of tubercle bacilli, this committee still recommends the use of streptomycin two or three days a week, and PAS several times a day, as the chemotherapy of choice in the treatment of most patients with tuberculosis."

*Am. J. Tuberculosis*, 67:269, 1953.

## FREE LITERATURE SERVICE

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### Allergies

allergic reactions<sup>1</sup>, asthma<sup>2</sup>, asthma (bronchial)<sup>3</sup>, drug sensitivities<sup>4</sup>, eczema<sup>5</sup>, food<sup>6</sup>, hay fever<sup>7</sup>, urticaria<sup>8</sup>.

### Blood, Cardiovascular

anemia<sup>9</sup>, anemia (pernicious)<sup>10</sup>, anticoagulant<sup>11</sup>, arteriosclerotic peripheral vascular disease<sup>12</sup>, angina pectoris<sup>13</sup>, Buerger's disease<sup>14</sup>, cardiovascular disorders<sup>15</sup>, congestive heart failure<sup>16</sup>, cardiac asthma<sup>17</sup>, coronary artery<sup>18</sup>, coronary thrombosis<sup>19</sup>, chronic trench-foot<sup>20</sup>, dietetic restriction<sup>21</sup>, hypertension<sup>22</sup>, myocardial failure<sup>23</sup>, myocardial insufficiency<sup>24</sup>, peripheral neuritis<sup>25</sup>, Raynaud's disease<sup>26</sup>, thromboangiitis obliterans<sup>27</sup>, varicose vein<sup>28</sup>.

### Dermatology

acne<sup>29</sup>, athlete's foot<sup>30</sup>, bacterial dermatologic condition<sup>31</sup>, bed sores<sup>32</sup>, burns<sup>33</sup>, dermatoses<sup>34</sup>, eczema<sup>35</sup>, external ulcers<sup>36</sup>, fungus diseases<sup>37</sup>, infections<sup>38</sup>, ivy dermatitis<sup>39</sup>, pruritus<sup>40</sup>, topical infections<sup>41</sup>, yaws<sup>42</sup>.

### Endocrinology

adrenal gland<sup>43</sup>, cretinism<sup>44</sup>, diabetes<sup>45</sup>, exophthalmic goiter<sup>46</sup>, Graves' disease<sup>47</sup>, hyperthyroidism<sup>48</sup>, myxedema<sup>49</sup>, pitu-

itary gland<sup>50</sup>, thyroid gland<sup>51</sup>, thyrotoxicosis<sup>52</sup>.

### Eye, Ear, Respiratory

bronchitis<sup>53</sup>, choroiditis<sup>54</sup>, coughing<sup>55</sup>, eye infections<sup>56</sup>, ear infections<sup>57</sup>, iritis<sup>58</sup>, keratitis<sup>59</sup>, laryngitis<sup>60</sup>, nasal congestion<sup>61</sup>, night blindness<sup>62</sup>, otologic dermatosis<sup>63</sup>, pharyngitis<sup>64</sup>, respiratory infections<sup>65</sup>, sympathetic ophthalmia<sup>66</sup>, sinusitis<sup>67</sup>, tonsillitis<sup>68</sup>, uveitis<sup>69</sup>, visomotor rhinitis<sup>70</sup>.

### Gastrointestinal, Liver and Spleen

amebiasis<sup>71</sup>, colitis<sup>72</sup>, constipation (chronic)<sup>73</sup>, cirrhosis of liver<sup>74</sup>, constipation<sup>75</sup>, diarrhea<sup>76</sup>, gallbladder and bile ducts<sup>77</sup>, gastrointestinal spasm (functional)<sup>78</sup>, gastroduodenal bleeding<sup>79</sup>, peptic ulcer<sup>80</sup>, staphylococci<sup>81</sup>, streptococci<sup>82</sup>.

### Genito-Urinary

bladder diseases<sup>83</sup>, cystitis<sup>84</sup>, kidney diseases<sup>85</sup>, prostate gland<sup>86</sup>, pyelitis<sup>87</sup>, ureter diseases<sup>88</sup>, urinary tract infections<sup>89</sup>, urethra diseases<sup>90</sup>.

### Geriatrics

anemia<sup>91</sup>, arteriosclerosis<sup>92</sup>, cardiac edema<sup>93</sup>, chronic fatigue<sup>94</sup>, climacteric



(male) <sup>95</sup>, constipation <sup>96</sup>, insomnia <sup>97</sup>, low blood sugar level <sup>98</sup>, protein deficiency <sup>99</sup>, senility (male) <sup>100</sup>, senility (female) <sup>101</sup>, vitamin deficiencies <sup>102</sup>.

## Gynecology and Obstetrics

amenorrhea <sup>103</sup>, cervicitis <sup>104</sup>, climacteric (female) <sup>105</sup>, conception control <sup>106</sup>, dysmenorrhea <sup>107</sup>, female disorders <sup>108</sup>, habitual abortion <sup>109</sup>, leukoplakia (vulvar) <sup>110</sup>, leukorrhea <sup>111</sup>, menopause <sup>112</sup>, menometrorrhagia <sup>113</sup>, premenstrual <sup>114</sup>, disorders <sup>115</sup>, postpartum bleeding <sup>116</sup>, pregnancy (nausea & vomiting) <sup>117</sup>.

## Infectious Diseases

brucellosis <sup>118</sup>, pneumonia (primary, atypical) <sup>119</sup>, Rocky Mountain spotted fever <sup>120</sup>, tuberculosis <sup>121</sup>.

## Neuromuscular

analgesic <sup>122</sup>, joint and muscle pain <sup>123</sup>, muscle dysfunction <sup>124</sup>, muscle spasm <sup>125</sup>, multiple sclerosis <sup>126</sup>, neuralgia ischiatica <sup>127</sup>, neuritis, diabetic <sup>128</sup>, osseous and neuromuscular disturbances <sup>129</sup>, Parkinsonism <sup>130</sup>.

## Nutrition

anemia <sup>131</sup>, avitaminoses <sup>132</sup>, impaired fat metabolism <sup>133</sup>, malnutrition <sup>134</sup>, mineral deficiencies <sup>135</sup>, obesity <sup>136</sup>, multiple vitamin deficiencies <sup>137</sup>, pellagra <sup>138</sup>, protein deficiency <sup>139</sup>, vitamin deficiencies <sup>140</sup>, multiple deficiencies <sup>141</sup>.

## Pediatrics

bowel habits <sup>142</sup>, diarrhea <sup>143</sup>, diaper dermatitis <sup>144</sup>, ear infections <sup>145</sup>, formula <sup>146</sup>, infantile eczema, nutritional needs <sup>147</sup>, scurvy <sup>148</sup>.

## Rheumatic and Arthritic Diseases

arthritis <sup>149</sup>, bursitis <sup>150</sup>, gout <sup>151</sup>, gouty arthritis <sup>152</sup>, musculoskeletal pain <sup>153</sup>, rheumatic disease <sup>154</sup>, rheumatic fever <sup>155</sup>, rheumatoid arthritis <sup>156</sup>.

## Miscellaneous

alcoholism <sup>157</sup>, barbiturate poisoning <sup>158</sup>, debridement of necrotic tissue <sup>159</sup>, edema <sup>160</sup>, edema (salt retention) <sup>161</sup>, industrial dermatoses <sup>162</sup>, meningitis <sup>163</sup>, neuropsychiatry <sup>164</sup>, nervous tension <sup>165</sup>, psychoses <sup>166</sup>.



## Supraclavicular Nerve Block for the Painful Shoulder

Treatment of the painful shoulder, both acute and chronic, is by injections into the suprascapular nerve, the aim of the treatment being to eliminate pain and restore active movement. The rationale of the injections is that the analgesic block is said to interrupt the vicious circle of pain which is present in various shoulder conditions, such as calcification about the shoulder-joint, biceps tendinitis, tears of the musculotendinous cuff, the shoulder-hand syndrome, "frozen shoulder," degenerative shoulder lesions and even cervical root pain.

The technique of these injections is shown diagrammatically. The nerve is injected as near to the suprascapular notch, as possible, and

the analgesics that have been used are 1 per cent procaine and 1 per cent or 2 per cent lignocaine in doses of 10 to 20 ml.

It is claimed that this method of nerve block is a very useful adjunct in the treatment of these shoulder conditions. It is not effective in all cases, and in some instances repeated nerve blocks may be necessary. The procedure is simpler, however, than stellate ganglion block and gives equally satisfactory results; it also has fewer complications. Sympathetic nerve block is necessary only for lesions distal to the elbow, in the author's opinion.

J. L. Goldner, *South. Med. J.*, 45:1125, 1952.



## NEW PHARMACEUTICAL PRODUCTS

### Potassium Chloride Emplet

(Parke-Davis)

Each tablet contains potassium chloride, 5 grn. *Indications:* In treatment of potassium deficiency. *Dosage:* Two to 4 tablets 1 to 4 times daily. *Supplied:* In bottles of 100 and 1,000 tablets.

### Pyraldine No. 2

(Van Pelt & Brown)

Antihistaminic, decongestive cough expectorant. *Dosage:* Initially, 2 teaspoonfuls followed by 1 teaspoonful every 4 hours. *Supplied:* bottles of 16 fl. oz.

### Biicillin

(Wyeth)

Suspension of dibenzylethylene-diamine dipenicillin G in a flavored, aqueous syrup base containing 150,000 units per teaspoonful. *Indications:* Treatment of Penicillin-susceptible infections in children, or as prophylaxis against rheumatic fever and secondary infection following tonsillectomy, tooth extraction or other surgery. *Dosage:* As directed by physician. *Supplied:* bottles of 2 fl. oz.

### Bristamin APC Tablets (Bristol)

Each tablet contains Bristamin Dihydrogen citrate acetylsalicylic acid, 0.21 gm.; phenacetin, 0.15 gm.; caffeine, 0.03 gm. *Indications:* treatment of rhinorrhea and allergic-like symptoms accompanying the common cold. *Dosage:* As directed by physician. *Supplied:* bottles of 100 and 1,000 tablets.

### Calcium Disodium Versenate

(Riker)

Preparation of calcium chelate of Ethylenediamine Tetraacetic Acid. *Indications:* treatment of acute and chronic lead poisoning. *Dosage:* intravenously as directed by physician. *Supplied:* 5 cc. ampuls, boxes of 6.

### Deltamide W/Penicillin (Armour)

Each tablet or teaspoonful contains: sulfadiazine, 0.167 Gm.; sulfamerazine, 0.167 Gm.; sulfamethazine, 0.056 Gm.; sulfacetamide, 0.111 Gm. and potassium penicillin G, 250,000 Units. In infections due to group A beta hemolytic streptococci, pneumococci, meningococci, gonococci, some staphylococci and other microorganisms sensitive to sulfonamides and penicillin. *Dosage:* As directed by physician. *Supplied:* Tablets in bottles of 36 and 100, suspension in bottles of 2 oz.

### Gynetone (.02 and .04) Repetabs

(Schering)

"02" contains 0.02 mg. ethinyl estradiol plus 5 mg. methyltestosterone, the ".04" contains 0.04 mg. ethinyl estradiol plus 10 mg. methyltestosterone. *Indications:* For treatment of the menopause and osteoporosis, management of geriatric patients where hormonal supplementation is desirable. *Dosage:* As directed by physician. *Supplied:* bottles of 30 and 100.

## Interrelationships of Serum Lipids and Their Bearing on Atherosclerosis

Serum lipid levels were determined in 38 male and 91 female inmates—all over 65 years of age and with no history of major illness. The women possessed a significantly higher amount of Sf 10-20 molecules than the men. The only two correlations which were found to be statistically significant were the correlation in men between Sf 10-20 molecules and total cholesterol, and in women, the correlation between Sf 10-20 molecules and age. The serum total-cholesterol level is thus a much better guide to the degree of atherosclerosis in males than in females.

This investigation supports the observation of Gofman that the amount of Sf 10-20 molecules does not change in males after the middle 30's, but that it continues to rise steadily with age in females.

The high serum lipid levels in the female may be associated with the female sex hormones. Previously it was thought that a close relationship existed between the Sf 10-20 molecules and the degree of atherosclerosis, but the higher figures for Sf 10-20 molecules in the females in this series do not support that assumption.

M. M. Gertler, B. S. Oppenheimer, *Circulation*, 7:533, 1953.

## C.P.T.<sup>®</sup> Chemical Pregnancy TEST

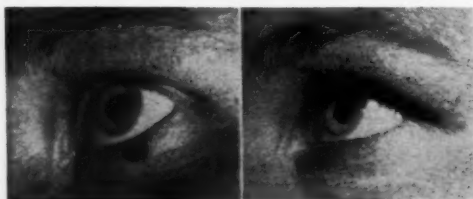
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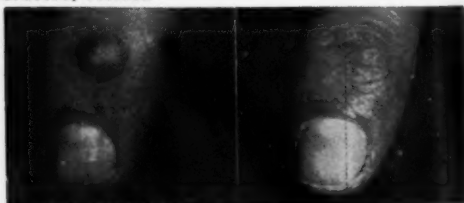
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▶ This patient's father, a physician, wanted to remove this synovial cyst with the knife. Patient refused, but submitted readily to Bichloracetic Acid therapy. A single treatment, drilling the acid into the center of the lesion sufficed. No scar, no pain and no patient resistance.



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# PSORIASIS

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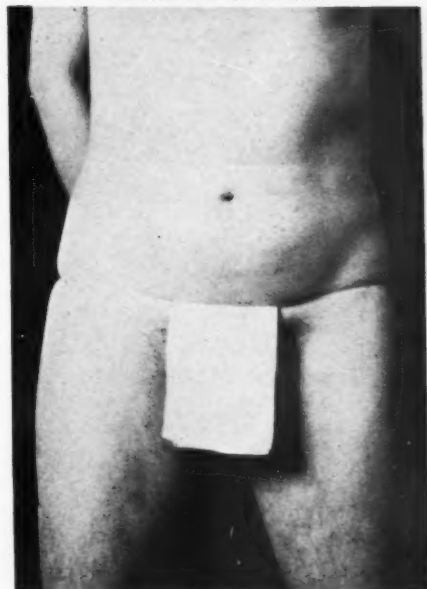
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## Etiology and Management of Spontaneous Pneumothorax

It is very often difficult to establish the exact pathogenesis of spontaneous pneumothorax. This entity is perhaps best described as a pneumothorax resulting from a bronchio-tree-pleura space communication not established by direct laceration of intervening tissues. In 64 per cent of the authors' cases the condition was labeled "idiopathic." Certain factors are known to be of etiologic significance, and cases can be classified most conveniently under the following headings: (1) structural cystic lung changes; (2) inflammation; (3) emphysema; (4) trauma; and (5) idiopathic pneumothorax.

In many if not all of these cases of spontaneous pneumothorax the condition was caused by rupture of subpleural blebs or bullae which may have been congenital or the result of local structural changes produced by obstructive emphysema, pneumonitis, cystic bronchiectasis or tuberculosis. Tuberculosis is an infrequent cause (6 per cent). A history of indirect trauma preceding the collapse is unusual.

Insertion of a Pezzer catheter into the pleural cavity with water-seal drainage can easily be performed with the patient under local anesthesia. The advantages of such treatment are more rapid re-expansion of the lung, early relief of symptoms, prevention of complications, reduction in hospitalization time, and earlier return to economic productivity.

Finally, it should be pointed out that thoracotomy and definitive surgery, such as resection blebs, segments, or lobes, are indicated in progressive hemopneumothorax, persistent bronchopleural fistula, and multiple recurrences.

R. L. Rapport, et al, *Arch. Surg.*, 67:266, 1955.